A Literature Review - Problem Definition Studies on Selected Toxic Chemicals

Volume 4 of 8

OCCUPATIONAL HEALTH AND SAFETY ASPECTS OF THE FOG OILS SGF NO. 1 AND SGF NO. 2 AND SMOKE SCREENS GENERATED FROM THEM

Final Report - April, 1978

by

Deborah Liss-Suter
Jon E. Villaume, Ph.D.

Principal Investigator

Paul N. Craig, Ph.D.

Reviewed by

Frederick J. Goldstein, Ph.D.

Supported by

U.S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD-17-77-C-7020

Project Officer

Captain Ronald N. Shiotsuka, Medical Services Corps
Environmental Protection Research Division
U.S. Army Medical Bioengineering Research and Development Laboratory
Fort Detrick, Frederick, Maryland 21701

Approved for Public Release; Distribution Unlimited

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

SCIENCE INFORMATION SERVICES DEPARTMENT
THE FRANKLIN INSTITUTE RESEARCH LABORATORIES
THE BENJAMIN FRANKLIN PARKWAY • PHILADELPHIA, PENNSYLVANIA 19103

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER

2. GOVT ACCESSION NO

3. RECIPIENT'S CATALOG NUMBER

4. TITLE (and Subtitle)
A Literature Review - Problem Definition Studies on Selected Toxic Chemicals. Volume 4, OCCUPATIONAL HEALTH AND SAFETY ASPECTS OF THE FOG OILS SGF NO. 1 AND SGF NO. 2 AND SMOKE SCREENS GENERATED FROM THEM

5. TYPE OF REPORT & PERIOD COVERED
Final Report, Mar 77 - Apr 78

6. PERFORMING ORG. REPORT NUMBER

7. AUTHOR(s)
Deborah Liss-Suter, Principal Investigator: Paul N. Craig
Jon E. Villaume

8. CONTRACT OR GRANT NUMBER(s)
DAMD-17-77-C-7020

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Science Information Services Department
The Franklin Institute Research Laboratories
The Benjamin Franklin Parkway - Phila. PA 19103

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
62720A
3E762720A835 00.030

11. CONTROLLING OFFICE NAME AND ADDRESS
U.S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701

12. REPORT DATE
Apr 78

13. NUMBER OF PAGES
163

14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)
162 p.

15. SECURITY CLASS. (of this report)
UNCLASSIFIED

15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; Distribution unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

aerosol	fog oil	human toxicity	mammalian metabolism
analysis	fuel oil	industrial standards	mammalian toxicity
carcinogenicity	heating oil	kerosene	mineral oil
diesel fuel	human metabolism	lubricating oil	motor oil

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Literature is reviewed (144 references) on the following subjects: physico-chemical properties; generation of fog oil smoke; human toxicity, occupational hazards and associated health and safety practices and standards; toxicological investigations in animals including mice, rats, guinea pigs, hamsters, monkeys, rabbits, dogs, cats and calves; absorption, distribution, metabolism and excretion in mammals; methods of sampling and determining atmospheric fog oil smoke, and extraction and determination of oils in biologic

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

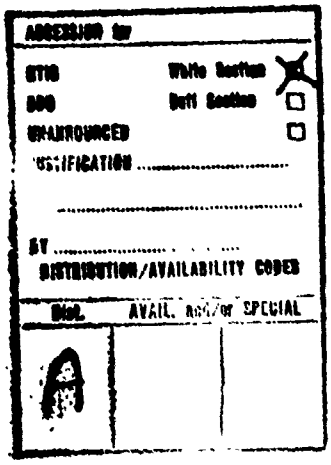
420 744

19. KEY WORDS (CONT.)

mutagenicity	polycyclic aromatic hydrocarbons
occupational disease	sampling
oil smoke	SGF No. 1
petroleum distillate	SGF No. 2
physicochemical properties	smoke/obscurant

20. ABSTRACT (CONT.)

media. The two fog oils, SGF No. 1 and SGF No. 2, are both refined petroleum products. SGF No. 1 is representative of fuels (similar to fuel oils #1 and #2 and light grades of diesel fuel), while SGF No. 2 is a lubricating oil (related to light automotive and industrial lubricating oils and mineral oils). The two fog oils have different viscosities, distillation ranges, flash points, and different hydrocarbon compositions, among others. Both oils are used in smoke generators, which vaporize the oils and force the vapors into the atmosphere, where they condense into a dense white smoke screen consisting of oil microdroplets. Effects of continuous exposure of U.S. Army personnel to fog oil smoke screens, for weeks on end, have not been documented. Industrial exposures to oils and oil mists are responsible for dermatoses, in the case of fuels, and for dermatoses, skin cancers and excess second primary tumors of the skin, respiratory tract and larynx, in the case of lubricating oils. In animals exposed to oil mists, oil pneumonias, paraffinomas and toxic systemic effects have been noted. Lubricating oil skin and pulmonary tumors are reported. Mutagenic effects are noted for intermediary metabolites of polycyclic aromatic hydrocarbons found in SGF No. 2. Avoidance of exposure of personnel to these oils, or the use of oils from which the carcinogenic polycyclic aromatic hydrocarbons have been extracted, along with appropriate medical surveillance, are recommended. Further research into the chemical composition of SGF No. 1 and SGF No. 2, and specific animal toxicological investigations using these analyzed oils are warranted.



EXECUTIVE SUMMARY

This literature review (144 references) discusses the problems related to fog oil exposure of humans and other mammals including rats, mice, guinea pigs, dogs, cats, hamsters, livestock and rhesus monkeys. There are two fog oils: SGF No. 1 and SGF No. 2. SGF No. 1 fog oil is a fuel oil distilled from crude petroleum, very similar to home heating oil, diesel fuel and some kerosenes. SGF No. 2 fog oil is a lubricating oil originating from crude petroleum, very similar to S.A.E. 10 motor oil and some industrially used lubricants and cutting oils. Its yellow color indicates that it is less refined than white mineral oil, a once commonly used laxative. Both fog oils can be used in smoke pots and mechanical smoke generators which produce dense white smoke screens. The smoke is actually made up of microdroplets of fog oil.

Army personnel who worked under fog oil smoke screens in World War II may be examined to learn whether or not there are long-term health hazards from fog oil smoke. In industry, workers exposed to lubricating oil mists frequently have skin conditions such as acne. Skin cancer also has been reported in these workers, as well as other cancers in the lung and throat. On the other hand, workers exposed on the job to heating or fuel oil mists usually complain only of skin irritations.

The inhalation of oil mists of SGF No. 1 fog oil caused lung tumors in mice and stomach tumors in monkeys. The oil accumulated in the lungs, but did not usually cause pneumonia. When exposed to oils similar to SGF No. 1, animals have developed pneumonias, adverse effects on the blood and bone marrow, skin and eye irritation and hair loss, and death at high doses.

Laboratory animals exposed to lubricating oils like SGF No. 2 have developed skin and lung tumors. Breathing of oil mists caused oil to accumulate in the lungs. In addition, pneumonia, adverse effects on the liver, spleen, kidneys, colon, skin and heart have sometimes resulted.

Although information on the ways in which the body absorbs, metabolizes, stores and excretes the fog oils is incomplete, it is established that mutagenic substances are formed in the enzymatic breakdown of some aromatic petroleum hydrocarbons found in SGF No. 2 type oils.

Recommendations for the further study of adverse effects of fog oils in occupationally exposed humans and in laboratory animals include evaluations of carcinogenicity and other long-term effects. There is a need to measure the air concentrations of fog oil smoke produced from smoke generators or smoke pots during present-day military smoke screening operations. It is also recommended that individuals who are exposed to the fog oil smoke screens have protection against breathing the smoke and against wearing oily clothing next to the skin or scalp.

Methods of collection of fog oil smoke in the air and measuring the air concentration of fog oil are presented. In animal experiments, it is useful to measure the accumulation of oil in the lungs and other parts of the body

after fog oil exposures. Appropriate methods to make this oil more visible and to measure its accumulation in various organisms are included.

The environmental impact of using fog oil smoke screens is presented as a separate document included in this series of reports.

ABSTRACT

Literature is reviewed (144 references) on the following subjects: physico-chemical properties; generation of fog oil smoke; human toxicity, occupational hazards and associated health and safety practices and standards; toxicological investigations in animals including mice, rats, guinea pigs, hamsters, monkeys, rabbits, dogs, cats and calves; absorption, distribution, metabolism and excretion in mammals; methods of sampling and determining atmospheric fog oil smoke, and extraction and determination of oils in biologic media. The two fog oils, SGF No. 1 and SGF No. 2, are both refined petroleum products. SGF No. 1 is representative of fuels (similar to fuel oils #1 and #2 and light grades of diesel fuel), while SGF No. 2 is a lubricating oil (related to light automotive and industrial lubricating oils and mineral oils). The two fog oils have different viscosities, distillation ranges, flash points, and different hydrocarbon compositions, among others. Both oils are used in smoke generators, which vaporize the oils and force the vapors into the atmosphere, where they condense into a dense white smoke screen consisting of oil microdroplets. Effects of continuous exposure of U.S. Army personnel to fog oil smoke screens, for weeks on end, have not been documented. Industrial exposures to oils and oil mists are responsible for dermatoses, in the case of fuels, and for dermatoses, skin cancers and excess second primary tumors of the skin, respiratory tract and larynx, in the case of lubricating oils. In animals exposed to oil mists, oil pneumonias, paraffinomas and toxic systemic effects have been noted. Lubricating oil skin and pulmonary tumors are reported. Mutagenic effects are noted for intermediary metabolites of polycyclic aromatic hydrocarbons found in SGF No. 2. Avoidance of exposure of personnel to these oils, or the use of oils from which the carcinogenic polycyclic aromatic hydrocarbons have been extracted, along with appropriate medical surveillance, are recommended. Further research into the chemical composition of SGF No. 1 and SGF No. 2, and specific animal toxicological investigations using these analyzed oils are warranted.

FOREWORD

The U.S. Army Medical Research and Development Command has received the task of assessing occupational health and safety aspects of various chemicals to which army personnel may be exposed. Accordingly, this Problem Definition Study (PDS) has been prepared as part of this research program under contract number DAMD-17-77C-7020, in order to provide the published data relating to occupational health and safety aspects of fog oils, SGF No. 1 and SGF No. 2, and smokes generated from them. The subjects covered in this report include physical and chemical properties, methods of analysis, toxicological studies on humans and animals, metabolism, industrial hygiene and safety practices, among others. An appendix lists the sources examined to locate relevant information in the literature. Also included in the appendix is a list of various organizations contacted to obtain relevant information concerning fog oils and oil smokes.

This is the 4th in a series of eight reports prepared under this contract.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

I. INTRODUCTION

The use of screening smokes generated from fog oils by the U.S. Armed Forces in World War II and up to the present, exposes personnel to the oils and smoke for varying lengths of time. In order to develop safeguards relating to oil and oil smoke exposure in humans, this literature survey and problem definition study has been performed in an attempt to provide evidence of exposure-related health hazards.

The topic of fog oils encompasses two types of petroleum products, fuels and lubricants, whose differences in physicochemical and toxicological properties are of a greater magnitude than their similarities. For this reason, most of this monograph is divided into sections discussing SGF No. 1 and related fuels or SGF No. 2 and related lubricating oils. Actual studies employing the fog oils themselves are minimal or nonexistant for most of the topics which are presented. Models have been chosen to represent the two fog oils, in order to indicate probable characteristics and toxicological effects, but not to substitute for the greatly needed research into the toxicological results of exposure of humans and animals to these fog oil smokes under conditions designed to simulate actual military smoke screening operations.

This monograph covers the following topics: physical and chemical properties, human toxicity, toxicological studies in animals, absorption, distribution, metabolism and excretion in mammals including man, industrial standards and occupational safety and health measures, methods of sampling and analysis in air and biologic media, and recommendations for further research. The sources of information employed to locate relevant literature, including persons and organizations which were contacted in this endeavor, are listed in the appendix.

II. PHYSICAL AND CHEMICAL PROPERTIES

The U.S. Military has employed two petroleum derived oils for use in mechanical smoke generators. These have been termed smoke generating fog oil (SGF) No. 1 and No. 2. Only SGF No. 2 has been ordered by the U.S. Army for the last 3-4 years (1). The specifications for these oils will be presented, followed by a brief discussion of their preparation from crude petroleum oil, and their approximate composition.

A. Specifications for Fog Oils

The property requirements for both SGF No. 1 and SGF No. 2 are defined by Military Specification MIL-F-12070A, dated 10 May 1956 (2). These requirements are summarized in Table 1.

SGF No. 1 must meet requirements for viscosity, carbon residue, pour point, distillation range and neutralization number. Likewise, SGF No. 2 must have the appropriate viscosity, pour point, carbon residue, neutralization number and flash point. Because these property requirements dictate the type of treatment an oil receives they are important, either directly or indirectly, in determining its hydrocarbon composition. Therefore, definitions of these properties (3) are provided as footnotes to Table 1. Any petroleum distilled from crude petroleum oil, which contains no additives and meets requirements listed in Table 1 for SGF No. 1 or SGF No. 2 can be sold as the respective fog oil.

B. Production of Fog Oils

It is unlikely that petroleum is specially processed to prepare SGF No. 1 or SGF No. 2. Rather, the specifications of these two fog oils correspond to products prepared for other purposes and the fog oils are probably drawn from these stocks. A brief description of the processing follows:

These petroleum products are derived from crude oil; this starting material is a complex mixture containing thousands of aromatic, paraffinic, and cycloparaffinic hydrocarbons, with small amounts of sulfur containing, nitrogen containing and other types of compounds. Petroleum products are obtained by fractional distillation of the crude oil; depending on specific uses of petroleum products and special requirements of these uses, further processing is often required.

In one distillation procedure, crude oil is placed in a heater to vaporize hydrocarbons into the fractional distillation column. In this column the constituents are separated by boiling range; the more volatile a particular fraction is the higher it will appear in the column; the gases come off at the top; below the gases in height and volatility are: naphtha; raw gasoline; raw kerosene, diesel fuel and fuel oils No. 1 and 2, collectively referred to as middle distillate; and some higher boiling material called heavy gas oil, in that order. A non-volatile residue remains at the bottom. SGF No. 1 is in the middle distillate fraction.

TABLE 1.
Property Requirements for SGF No. 1 and SGF No. 2,
Military Specification MIL-F-12070A (2).

Property	Type SGF No. 1		Type SGF No. 2	
	Maximum	Minimum	Maximum	Minimum
Flash point,[a] °F	-	-	-	320
Viscosity, Saybolt Universal[b]				
At 100° F, (seconds)	-	-	110	100
At 210° F, (seconds)	60[c]	-	-	-
Carbon residue (Conradson),[d] percent	0.1	-	0.1	-
Neutralization number[e]	0.1	-	0.1	-
Pour point, °F[f]	0	-	-40	-
Vapor temperature, °F at:				
10 percent distillation	-	390	-	-
50 percent distillation	-	490	-	-
90 percent distillation	610	-	-	-

a. Flash point: The lowest temperature at which vapors arising from the oil will ignite momentarily upon application of a flame (3).

b. Viscosity: The measure of resistance to flow of a liquid. In Saybolt Universal units it is the time in seconds for 60 ml of oil to flow through a capillary tube in a Saybolt Universal viscometer, as described in ASTM method D 88 (3).

c. A viscosity of 65 sec., at 210°F will be the maximum permissible for oils having a viscosity index of 50 or more.

d. Carbon residue: The carbonaceous residue formed after evaporation and pyrolysis of the oil.

e. Neutralization number: The weight in mg of potassium hydroxide needed to neutralize the acid in 1 g of oil (3).

f. Pour point: The lowest temperature at which the oil will flow when chilled without disturbance under test conditions [ASTM D 97] (3).

In order to obtain lubricating oil fractions, a two-stage distillation procedure is utilized. The first distillation volatilizes fractions from gases through middle distillate. The non-volatilized portion is then distilled separately, under reduced pressure, to prevent thermal decomposition of the oil. The products of this second distillation are lubricating oils and residue (4). SGF No. 2 is in the lubricating oil fraction.

Catalytic cracking, reforming and related operations (polymerization, alkylation, hydrogenation, aromatization and isomerization) are used to convert fractions obtained from the original crude oil, which are of lower economic value (usually gases, less volatile distillates and residue) into a new oil richer in fractions of greater economic value, principally gasoline (4).

The stocks destined to become diesel fuel or fuel oils #1 or 2 and lubricating oils, especially automotive lubricants, undergo more or less further processing depending upon the source of the crude oil and end use, including (3, 4):

1. Deasphalting: reduces carbon residue in fuel and lube oils through extraction or precipitant action of solvents (e.g. propane, alcohol or esters) on asphaltic or resinous materials; sulfur and heavy metals may also be removed. This step may be necessary to meet the carbon residue requirements of SGF No. 1 and No. 2.

2. Treating or Refining: included here are a large number of solvent extraction processes. Aromatics, cycloparaffins and other materials may be selectively extracted from lubricating oil stocks to enhance viscosity characteristics (particularly viscosity index, which is a measure of the magnitude of viscosity change with temperature) and their stability to degradation. Likewise, aromatics, nitrogen, sulfur and unstable compounds that affect burning quality and engine cleanliness can be removed from diesel fuel. Feed to these processes has normally been deasphalted and may be subsequently dewaxed.

3. Dewaxing: wax (straight chained paraffins) in lubricating oils gives the product a high pour point; it reduces fluidity because of the formation of wax solids at low temperatures.

SGF No. 1 likely undergoes deasphalting and some solvent treatment. Likewise, to meet viscosity, pour point and carbon residue requirements oil destined to become SGF No. 2 may require deasphalting, solvent refining and dewaxing.

C. Composition of Fog Oils

There are few data on the composition of SGF No. 1 or SGF No. 2 per se. Therefore, petroleum products which correspond to fog oils in physical and chemical properties, due to the fact that they have come from the same distillation and treatment processes, will be discussed, in order to clarify the composition of the two fog oils.

There is no constant composition for any petroleum product. The composition of diesel fuels, fuel oils, SGF No. 1, SGF No. 2, lubricating oils, and others will vary from product to product and sample to sample. Two factors are important in producing this variation: crude oil source and refining processes.

Crude oils are complex mixtures containing thousands of paraffinic, cycloparaffinic and aromatic hydrocarbons, small amounts of sulfur compounds, nitrogen-containing compounds, other compounds and heavy metals. Crude oils from around the world are classed as paraffinic, naphthenic or asphaltic depending on whether the residues left after distillation are high in paraffins, cycloparaffins or aromatics; within these classifications there is wide variation from source to source.

The treatment the crude oil undergoes at the refinery also affects its composition. Catalytic cracking and related conversion processes favor the formation of olefins, aromatics and branched paraffins at the expense of other types of hydrocarbons. On the other hand, solvent treating or refining removes aromatics, cycloparaffins and olefins contained in cracked oils.

An attempt will be made to define the probable range of compositions for fog oils. However, the following information is only indicative of, and not meant to substitute for, an analysis of fog oil samples.

1. SGF No. 1

Distillation range, specific gravity, viscosity and pour point are very important in determining hydrocarbon composition. Of these, only distillation range and, secondarily, pour point would appear to contribute significantly to limiting the composition of SGF No. 1 (a maximum viscosity is specified, but this high value is not usually attained in products within this boiling range). SGF No. 1 is broadly defined, and therefore, wide variation in composition is possible.

SGF No. 1 corresponds in distillation range to other middle distillate fuels, such as diesel fuel and fuel oils No. 1 and 2, and other properties are consistent with these fuels. It likely comes from a feedstock originally destined to be one of these fuels, but it differs from diesel fuel as a minimum in that SGF No. 1 is almost pure hydrocarbon since it contains no additives. Hydrocarbon types and composition analyses of middle distillates in general as well as specific distillates, including heating oil, diesel fuel and kerosene are presented in Tables 2, 3 and 4, in the section entitled SGF No. 1 Models.

2. SGF No. 2

The SGF No. 2 supplied to the U.S. Army is drawn from a lubricant stock sold as a raw material to various industries (5). It is a light viscosity lubricant, sometimes called "100 pale oil" because it has a viscosity of 100 SSU at 100°F (equivalent in viscosity to a SAE 20 motor oil) (3) and is a pale or straw-colored liquid. In addition to the sources of variation mentioned above, the composition of SGF No. 2 is subject to further varia-

tion, because oil companies will draw from whatever stocks are available to fill an order which fits the requirements of the Military Specification (5).

D. SGF No. 1 and SGF No. 2 Models

The human and animal toxicology and metabolism sections have illustrated the effects of oils which are chemically, pharmacologically and toxicologically similar to SGF No. 1 or SGF No. 2, simply due to the fact that there is almost no available literature on SGF No. 1 or SGF No. 2. This subsection characterizes models for SGF No. 1 (diesel fuel, fuel oils No. 1 and 2, kerosene etc.) and models for SGF No. 2 (automotive and industrial lubricating oils, white and medicinal mineral oils).

1. SGF No. 1 Models

As discussed earlier in this section, SGF No. 1 is a distillate of crude oil which vaporizes in the same general temperature range as diesel fuel stock, kerosene, and fuel oils (heating oils); these fractions are called middle distillates. The middle distillates are further processed to meet different functional requirements, through blending with cracked distillates, solvent refining of kerosene, addition of ignition improvers to middle distillates destined to become diesel fuel, and addition of anticorrosive additives which protect metals coming in contact with the oils. But, minus the additives, the middle distillate products all have the same hydrocarbon composition, which only varies according to the crude oil source, since the refining procedures - prior to solvent extraction - have been identical (3, 4, 6).

Hydrocarbon composition of middle distillates, as shown in Table 2 is variable, depending on oil source, and degree of blending of straight run and cracked middle distillate materials.

A more detailed analysis of hydrocarbon types present in middle distillates is offered in Table 3, and Table 4 shows the carbon numbers of the various aromatic hydrocarbons in middle distillate fuels.

Models used in the toxicology and metabolism sections of this report include kerosene, heating oils (fuel oil No. 1 and No. 2) and diesel fuel. These will be described below.

a. Kerosene

Kerosene can be produced from almost any refinery stream, that is, crude oil, thermally or catalytically cracked oil, or mixtures of these. The kerosene fraction usually boils in the same distillation range as the middle distillates, but may have a wider range, depending on the refinery's operation as well as on the customer's needs (4). The kerosene distillate is usually treated with sulfuric acid, followed by solvent extraction to remove aromatic compounds and sulfur compounds. (Aromatics are undesirable because of the smoky flame produced when kerosene is burned. The sulfur compounds tend to form incrustations on lamp wicks) (3, 4). Synonyms for kerosene are range oil or illuminating oil. Deodorized kerosene is super-refined, containing less than 4% aromatic hydrocarbons (7).

TABLE 2

Variation in Hydrocarbon Composition of Middle Distillates

Hydrocarbon type	Range (in wt.%)	Reported values (in wt.%)															
		a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p
Saturated paraffins	34.6–90	37–43	34.6	60	35	25	–	74	71–76	75	60	78.9	22.8	72.6	77	50	80.4
Cycloparaffins		26–32		30	55	50	65						14				
Aromatics	10–58	30–32	57.5	10	15	25	33	26	24–29	25	40	19.5	58	27	23	50	19.6
Unsaturates	0–7.5	–	7.5	–	–	–	2	–	–	–	–	1.6	5.2	0.4	–	–	–

Refs:

a = Fuel oil No. 2, Gerarde (8); b = Cracked middle distillate, Snyder (9); c = Paraffin-base kerosene, Bland and Davidson (3); d = Paraffin-base middle distillate, Bland and Davidson (3); e = Aromatic-base kerosene, Bland and Davidson (3); f = Aromatic-base middle distillate, Bland and Davidson (3); g = Diesel fuel, Herlan (10); h = Middle distillate, Fodor and Newman (11); i = Straight-run diesel fuel, Ehrler et al. (12); j = Middle distillate, Ehrler et al. (12); k = Diesel fuel, Kearns (13); l = Fuel oil No. 2, Kearns (13); m = Diesel fuel, Keen (14); n = Straight-run middle distillate, Fitzgerald et al. (15); o = Cracked middle distillate, Fitzgerald et al. (15); p = Middle distillate, Mair and Mayer (16).

TABLE 3

Hydrocarbon Type Analysis of Middle Distillates

Hydrocarbon type C_{11}-C_{20} range	Reported values, wt.% a	b	c	d	e
n- and isoparaffins	40-52	21.4	22.8	43	28
monocycloparaffins	18-25	13.0	10.3	21	12
non-condensed dicycloparaffins	6-12				
non-condensed tricycloparaffins	1-5				
condensed dicycloparaffins	0-2	4.8	3.7	9	7
condensed tricycloparaffins				3	2
alkylbenzenes	3-11	9.8	20.8	5	9
indanes, tetralins	2-7	10.6	8.9	4	7
indenes, dihydronaphthalenes	0-4	3.0	1.9	2	1
naphthalene	3-11	0.2	0.2	7	20
alkylnaphthalenes		18.9	21.1		
acenaphthalenes, other $C_{17}H_{2n-14}$	0-3	6.7	4.0	3	6
acenaphthylenes, fluorenes, other $C_{17}H_{2n-16}$	0-3	2.8	.8	2	4
tricyclic aromatics, phenanthrenes, C_nH_{2n-18}	0-3	1.2	0.3	1	4
Olefins	-	6.6	5.2	-	-

Refs:

a = Middle distillate, Ehrler et al. (12); b = Diesel fuel, Kearns (13); c = Fuel oil No. 2, Kearns (13); d = Straight-run middle distillate, Fitzgerald et al. (15); e = Cracked middle distillate, Fitzgerald et al. (15).

TABLE 4

Carbon Number Distribution by Volume % of Aromatic Hydrocarbons Present in Fuel Oil #2, Kerosene and Diesel Fuel Samples

Benzenes	Fuel oil #2	Kero-sene	Diesel fuel
C_9	0.5	0.3	0.2
C_{10}	1.7	1.4	0.5
C_{11}	3.3	1.6	1.0
C_{12}	5.3	1.0	1.8
C_{13}	4.8	0.8	1.8
C_{14}	2.7	0.5	1.4
C_{15}	1.4	0.3	1.0
C_{16}	0.7	0.2	0.7
C_{17}	0.3	-	0.6
C_{18}	0.1	-	0.4
C_{19}	-	-	0.2
C_{20}	-	-	0.2
Indanes			
C_9	-	-	0.1
C_{10}	0.5	0.2	0.3
C_{11}	2.3	1.0	1.5
C_{12}	2.8	1.5	2.8
C_{13}	1.8	1.2	2.5
C_{14}	0.9	0.7	1.5
C_{15}	0.4	0.3	0.8
C_{16}	0.2	0.1	0.5
C_{17}	-	-	0.3
C_{18}	-	-	0.2
C_{19}	-	-	0.1
Indenes			
C_9	-	-	0.1
C_{10}	-	-	0.1
C_{11}	0.3	-	0.3
C_{12}	0.5	0.1	0.5
C_{13}	0.5	0.2	0.6
C_{14}	0.3	0.2	0.6
C_{15}	0.2	0.1	0.4
C_{16}	0.1	-	0.2
C_{17}	-	-	0.1
C_{18}	-	-	0.1

Naphthalenes	Fuel oil #2	Kero-sene	Diesel fuel
C_{10}	0.2	0.1	0.2
C_{11}	2.5	0.6	1.6
C_{12}	6.7	1.5	4.8
C_{13}	6.8	1.0	5.6
C_{14}	3.4	0.3	3.5
C_{15}	1.2	0.1	1.7
C_{16}	0.4	-	0.9
C_{17}	0.1	-	0.5
C_{18}	-	-	0.2
C_{19}	-	-	0.1
Acenaphthenes			
C_{12}	0.1	-	0.1
C_{13}	0.9	-	0.9
C_{14}	1.4	0.1	2.2
C_{15}	1.0	-	2.2
C_{16}	0.4	-	1.4
C_{17}	0.2	-	0.6
C_{18}	-	-	0.2
C_{19}	-	-	0.1
Acenaphthylenes			
C_{13}	-	-	0.1
C_{14}	0.2	-	0.3
C_{15}	0.3	-	0.7
C_{16}	0.2	-	0.8
C_{17}	0.1	-	0.5
C_{18}	-	-	0.3
C_{19}	-	-	0.1
Anthracenes, Phenanthrenes			
C_{14}	0.1	-	0.1
C_{15}	0.1	-	0.3
C_{16}	0.1	-	0.4
C_{17}	-	-	0.3
C_{18}	-	-	0.1

Ref: Kearns (13). These percentages are averages of two or more samples each.

b. Fuel oils

There are 6 grades of fuel oils, of which fuel oil No. 1 and fuel oil No. 2 are distillates boiling in the range characteristic of the middle distillates. Fuel oil No. 1 is used in vaporizing pot-type burners, while No. 2 is general purpose domestic heating oil. Like SGF No. 1 fog oil, fuel oils are usually blends of straight run and cracked distillates which are byproducts of gasoline manufacture (4). Domestic fuel oil No. 2 is generally a straight run distillate of crude oil while industrial fuel oil No. 2 is usually a blend of straight and cracked distillates.

c. Diesel fuels

Diesel fuels come in four grades, of which the first two are products of the middle distillate oils. These are used in high-speed engines, such as in tractors, trucks and buses. Other grades of diesel fuel are more viscous, containing blends of higher-boiling distillates and some residual (non-volatile) fuels (3). The latter are used in low-speed engines operating with sustained loads at constant speeds, such as large marine and railroad diesel engines.

Performance properties of diesel fuels include ignition quality. A high cetane number (n-hexadecane content) for a fuel gives relatively easier starting at low temperatures. Most straight run diesel fuels have naturally high cetane numbers, but if the crude oil was rich in aromatic compounds, or if the distillate fuel is a blend of straight and cracked distillates, lower cetane numbers result. Cetane improvers are therefore added to diesel fuels, or alternatively, solvent refining to remove aromatic compounds may be employed to raise the cetane number. Organic nitrates and peroxides (amyl nitrate, hexyl nitrate, acetone peroxide) are additives used to improve the ignition quality of diesel fuels (4). As little as 0.1-0.3% by volume of amyl nitrate is sufficient to upgrade blended distillates into diesel fuels of acceptable cetane numbers (3).

Additives also are utilized to inhibit corrosion of fuel storage containers and copper fittings, and to deter gum formation in the diesel engine (3).

2. SGF No. 2 Models

SGF No. 2, being a light lubricating oil, is similar in most respects to automotive lubricants and some industrial lubricating oils of similar viscosities. A higher degree of refining will convert these straw colored "pale" oils to "white" oils, which is now mandatory in some industrial applications. White oils also have medicinal uses (adjuvant, laxative, cosmetic).

Lubricant oils generally have a boiling range of 300-800°C. The hydrocarbons constituting these oils generally contain 20-50 carbon atoms (6), and based upon its viscosity SGF No. 2 probably is made up mainly of hydrocarbons in the molecular weight range of 240-420 atomic units (3).

After the lubricant oil stock is obtained from fractional distillation it is deasphalted to remove constituents which would contribute to carbon residue. At this point it consists of aromatic, cycloparaffinic and mixed aromatic-cycloparaffinic hydrocarbons, which contain paraffinic side chains [often 7-20 carbon atoms in length] (6). Lubricant oils which have reached this stage of refinement might be expected to yield a distribution of hydrocarbon types in the range summarized in Table 6. The content of aromatic rings in untreated lubricating oil fractions generally varies from 10 to 30%, although 40% has been reported (6). However, the aromatic hydrocarbons of lubricating stocks produce poor viscosity characteristics, and many are unstable toward oxidation, which transforms them into resinous and asphaltic products. These aromatic hydrocarbons may be extracted by various solvents. The remaining oil is enriched in branched paraffins and cycloparaffins. Usually dewaxing follows.

TABLE 5
Summary of Composition of Lubrication Oil Stocks

Average No. of Rings per Molecule	1.8 - 3.0
Weight Percent of Aromatic Rings	10 - 30
Weight Percent of Cycloparaffinic Rings	13 - 45
Weight Percent of Paraffinic Side Chains	45 - 76

Ref: Sachanan (6).

Lubricating oil distillates normally contain only up to 10% normal and branched alkanes. Typical paraffins present would contain about 25 carbon atoms, with at least one paraffinic side chain, C4 or longer, in the middle of the molecule. Cycloparaffins with up to 4 five or six-membered rings per molecule predominate (6).

The following lubricating oils are representative models for SGF No. 2.

a. Automotive Lubricating Oils

The SAE (Society of Automotive Engineers) motor oils, especially SAE 10 or SAE 20, correspond in viscosity to SGF No. 2 (3). The hydrocarbon content is variable, as previously discussed. One analysis revealed 2.6 µg/100 ml of benzo(a)pyrene in fresh motor oil (17).

The presence of additives in commercial lubricating oils makes them dissimilar to SGF No. 2, which is additive free.

b. Industrial Lubricating Oils

Mineral oils replaced sperm whale oil and seal oil as lubricants in the cotton mills in the late 1800's (18). The first mineral oil lubricants were poorly refined, and occupational exposure lead to skin cancer epidemics, until, in the 1930's, benzo(a)pyrene was extracted with sulfuric acid. More recent solvent refining techniques more or less completely remove all polycyclic aromatic hydrocarbons from the lubricating oils, turning the oils from "pale" to "white" in color.

Spindle oil is a light viscosity oil, used to lubricate cotton spindles and other moving machine parts. It may contain additives, and the degree of refining (pale to white) varies (18).

Batching oil is used in jute manufacture, out of which comes burlap and sacking materials. It varies widely in composition, within the limits of light lubricating oils (19).

Metal working and cutting oils may be pure lubricating oils, mixtures of lubricating oil, lard oil, additives among others, water-oil emulsions - called "soluble oils", or may be completely or partially synthetic polymer oils (3, 20, 21).

Even pure petroleum cutting oils and their mists are dissimilar to SGF No. 2 in that the heat generated at the cutting edge of the tools used in metalworking may form oil decomposition products such as SO_2 and H_2S, which are recognized skin irritants in themselves. [Thermal decomposition of SGF No. 2 in the smoke generator may occur (see Generation of Smoke).] In addition, the alloy of which the cutting edge is made contains metals such as cobalt, a known cutaneous sensitizer. As the cutting edge wears down, the oil bathing the tool will pick up the metals. The cutting oil is continuously recycled through the machine during the metalworking operations (22).

A petroleum cutting oil (lubricating oil) was analyzed qualitatively by chromatographic separation, liquid-liquid extraction, and spectroscopy. The following polycyclic aromatic hydrocarbons were identified: 3 rings (anthracene, phenanthrene); 4 rings (pyrene, fluoranthene, chrysene, benzo(a)fluorene, benzo(a)anthracene); 5 rings (perylene, benzo(e)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene); and 6 rings (benzo(g,h,i)perylene, indeno-1,2,3(c,d)pyrene, phenylene pyrene). A second cutting oil sample contained: pyrene, methylpyrene, chrysene, alkylchrysene, fluoranthene, benzo(a)anthracene, benzo(a)pyrene, benzo(b)fluoranthene and benzo(k)fluoranthene. Benzo(a)pyrene concentrations ranged from 0.6 µg/l to 160 µg/l in unused cutting (lubricating) oils, and values up to 500 µg/l were reported for used cutting oils (20).

Cook et al. (23) analyzed an industrial lubricating oil, after extracting the aromatic fraction, which represented 20% of the oil sample volume. Anthracene derivatives, separated with maleic anhydride, included 2,6- and 2,7-dimethylanthracene, 2,3,6-trimethylanthracene, 1,3,5,7-, 1,3,6,7-, and 2,3,6,7-tetramethylanthracene, and four unidentified tri- or tetramethylanthracenes. Picric acid and ethanol extraction yielded: 1,8-dimethylphenanthrene, 1,2,8-trimethylphenanthrene, tetramethylphenanthrene, tetra-

methylfluorene, 1-methylpyrene, 1,2-benzofluorene, 8-methyl-1,2-benzofluorene, 1,8-dimethyldibenzothiophene, 1,2,6,7-tetramethyldibenzothiophene, 3-ethyl-6,8-dimethylnaphtho(1,2-b)-thiophene and pentamethylcarbazole. No quantitative data were presented.

Newspaper printing ink consists of a suspension of carbon black in white mineral (lubricating) oil (24). Pressrooms usually have visible oil mists due to the printing process which generates the mists (24). The degree to which this particular white oil has been refined was not reported.

Oils used to spray livestock and agriculture with pesticides, insecticides and other chemicals, may be either pale or white lubricating oils of a light viscosity (25).

c. Medicinal Mineral Oil

This is a transparent, colorless, almost odorless and tasteless liquid, highly solvent refined and composed of 100% non-aromatic, saturated hydrocarbons.

Synonyms include liquid paraffin, liquid petrolatum, U.S.P. mineral oil, white mineral oil and vaseline oil (26).

Mineral oil used as a laxative is slightly more viscous than SGF No. 2. Another less viscous white oil is used in oily nose drops and other preparations.

Two independent analyses of white mineral oils were found in the literature. Wagner et al. (27) reported the hydrocarbon composition of a medicinal mineral oil with a molecular weight of 350-410, with molecules containing 25-30 carbon atoms. Boitnott and Margolis reported the mean hydrocarbon composition of six mineral oil samples, by mass spectroscopy (28). The results of the analyses are presented in Table 6. The wide variation in alkane content is not unusual, considering the possible differences in source and refining that characterized the oils.

According to Hasserholt (29) traces of aromatic hydrocarbons in white oils can be determined by ultraviolet absorption or by separation and X-ray fluorescence.

E. Generation of Smoke

Smoke weaponry in World War II and the Korean War was used for large-area screening of rear-area targets, beach landings, paratroop assaults and other moderate to large tactical operations. The mechanical smoke generator was developed for these purposes. The first generator, M1 was a domestic oil burner, weighing 25,000 kg, and transported by barge, trailer or truck. It consumed 380 liters of fog oil, 570 l of water and 30 l of fuel an hour. The M2 was smaller and lighter in weight, and consumed 190 l of fog oil, and 19 l each of fuel and water per hour (30). The M3 is a pulse-jet engine generator which does not require water, and can be easily carried by 2 people. Consumption is 150 l of fog oil and 11 1/2 l of gasoline per hour (31). All of the mechanical generators are designed to produce a continuous smoke screen.

TABLE 6.
Hydrocarbon Composition of White Mineral Oils

Hydrocarbon Type	% (mean of 6 samples)[a]	%[b]
Straight and branched alkanes	26.8	5.1
Cyclic alkanes		
noncondensed (1 ring)	26.8	27.0
condensed		
2 rings	22.1	23.9
3 rings	13.6	19.8
4 rings	6.7	13.3
5 rings	2.9	6.9
6 rings	0.9	4.0
Aromatic hydrocarbons	0	0

Refs: a = Boitnott and Margolis (28)

b = Wagner et al. (27)

Smoke pots and smoke grenades emit a small volume of smoke for a short time. Floating smoke pots are designed to emit a dense cloud for about 10 minutes (32). A combustible material and an oxygen source are necessary to produce smoke in this way.

The large generators, used to achieve continuous screening, require a heat source to vaporize (not burn) the fog oil, an atomizer to accelerate the vaporization, a blower or pump to rapidly move the vaporized oil away from the heat source, and an oxygen-poor chamber to prevent explosion or combustion of the concentrated oil vapors. These requirements are met in the exhaust manifold of an internal combustion engine, automobile engine, heat engine or steam boiler (33).

The M3A3 pulse-jet generator is a gasoline engine with a pump assembly, driven by the exhaust gases, which draws the fog oil from an external storage drum and pumps it into the engine tube. Vaporization occurs as the fog oil is mixed with hot engine exhaust gases and the vapors are forced into the atmosphere at a high velocity, passing through 3 outlet nozzles. As the vapors meet the cooler atmosphere, they are condensed into small droplets of liquid oil (34).

The temperature at the discharge nozzles of various mechanical generators may reach 540°C, but no thermal breakdown or ignition of vapors was found to occur at this point because the high escape velocity allows only a very short duration of contact of the vapors with the nozzles (35). A test hydrocarbon, n-hexadecane, heated for six hours at 371 or 399°C in a closed system containing various metal surfaces showed about 4% or more thermal decomposition. New compounds formed ranged from C_1-C_{16} and higher, plus hydrogen. It was found that pyrolysis of naphthenes was more rapid than n-hexadecane at 371°C, the weakest naphthene bind being the ring-side chain juncture (36). The possibility of thermal decomposition of fog oil exists, but the conditions which may enhance pyrolysis and the extent of pyrolysis are unknown.

The mixing of fog oil vapors with exhaust gases also presents a problem. The less volatile exhaust components will probably condense with the fog oil vapors, while lighter molecular weight hydrocarbons remain as gases and escape into the atmosphere. The concentration of exhaust components in the vaporized and/or condensed fog oil is not known.

The atmosphere immediately condenses the vaporized fog oil into small liquid droplets. The discharged fog should feel cool and dry to the naked hand held about one meter from the point of emergence (35). A good smoke screen makes the disc of the sun appear light orange or pink. A droplet diameter of 0.5-1.0 μ is desirable for maximum scattering of visible light (31). The average droplet size is controlled by the rate of cooling as well as the vapor concentration.

The condensed oil droplets form a stable dispersion similar to a natural fog or mist. It does not convert back into the gaseous phase (33). The smoke settles very slowly, due to the small droplet size. It may remain afloat for an hour without coalescence or condensation, and be carried as far as 6.5 km, depending only on meteorological conditions (30, 35).

Direct information on the concentration of the oil droplets in air is lacking. A private communication from FMC Corporation indicated a possible exhaust vapor concentration of approximately 46,000 mg/m^3. Visibility in the smoke may be reduced to one meter or less, according to Naval Systems Sea Command and U.S. Army private communications.

III. HUMAN TOXICITY

The human toxicology of fog oil has not been medically documented for the armies which were hidden amidst the dense white smoke screens over parts of Italy and northern Europe during World War II. The reason for this lack of information may very well be that any adverse effects were not severe enough to warrant medical attention, or that the effects were too general or undiagnostic to be attributed to oil smoke. Nevertheless, exposure to oil smoke did occur on a large scale. With this in mind, the subject has been investigated from the standpoint that the two fog oils, SGF No. 1 and SGF No. 2, are representative of fuel oils and lubricants, respectively Exposures to these "model" fuel oils and lubricants have been documented in the literature, and will be presented separately for SGF No. 1 and SGF No. 2.

A. Exposure of the U.S. Armed Forces to Fog Oil Smoke

Medical records of the Chemical Corps Historical Office were searched for reference to injurious effects of World War II fog oil smoke screening operations. There were no indications of any kind that smoke generator unit personnel suffered ill effects from exposure to their own fog oil smoke screens, nor was there any indication of precautions taken to avoid such exposure (37).

The Toxicology Division of the U.S. Army Edgewood Arsenal, Development and Engineering Directorate, Munitions Systems Division, upheld the position that there would be very little risk or danger in repeated and high level exposures to fog oil, based on the work done by medical researchers in the area, as well as on the fact that among entire armies living in a constant smoke screen of fog oil in Italy for weeks on end, there was no evidence of exposure related illness or carcinogenic or mutagenic effects from these operations (38).

The Toxicology Division of the U.S. Army Edgewood Arsenal further stated that although there was considerable experience with oil smokes at Anzio, Italy, and elsewhere, it was doubtful whether there had been adequate documentation and medical follow-up on personnel exposed to the oil smokes (39).

Not only are there no data on morbidity or mortality of army personnel who were exposed to oil smoke, there is also no available information on the atmospheric concentrations of the smoke screens to which the units were exposed. Living for weeks on end in an atmosphere dense with oil droplets, the armies could have been exposed to inhalation of oil droplets, as well as contamination of clothing, skin, food, water, and everything in their possesion which was taken out-of-doors. This extensive contamination would be probable, due to the settling down of the oil droplets onto available surfaces, leading to the formation of an oil film as droplets coalesced. Allowances must also be made for evaporation of oil mist droplets before and after settling, although neither the extent of evaporation nor of settling into films was documented.

B. SGF NO. 1 Models

There are no reports in the literature dealing specifically with the human toxicity of SGF No. 1. However, since it is a middle distillate, with properties similar to those of diesel fuel, heating oil and kerosene (as discussed in the Physical and Chemical Properties section of this report), toxic properties of these models will serve to elucidate the human toxicity of SGF No. 1 fog oil.

1. Acute Toxicity of Mists

Diesel fuel aerosols were used as a control atmosphere in a study of the effect of atmospheric pollutants (40). Normal subjects exposed to aerosol concentrations of 330 mg/m^3 and 170 mg/m^3 reported practically no eye, nose or throat irritation during the 10 minutes of exposure. Pulmonary effects were not considered.

Subjects inhaling deodorized kerosene (treated to remove most aromatics) mean vapor-air concentrations of 140 mg/m^3 (20 ppm) for 15 minutes reported no eye, nose or throat discomfort or irritation during or following the exposure (7). This concentration was the highest obtainable, representing saturation at 25°C. Other subjects inhaled a series of vapor-air concentrations of deodorized kerosene over a period of 2 days, with 10-second exposures to each sample. The odor threshold was determined to be approximately 0.6 mg/m^3 (0.09 ppm) for 83% of the subjects. With this practically aromatic-free hydrocarbon mixture (3.9% aromatics), there was essentially no irritation or toxicity due to inhalation of vapors.

Selected aromatic hydrocarbons, present in varying concentrations in the middle distillates, have been studied individually, in terms of their ability to irritate eyes, skin and respiratory passages. Alkylbenzenes have been found to be highly irritating when concentrated. Tetramethylbenzenes such as durene, in mist, or vapor form, are especially irritating substances (8).

Nau et al. (41) studied the effects of aromatic hydrocarbons boiling in the low end of the middle distillate range, characterized by carbon numbers C_9-C_{12}. Vapor concentrations of 137,500 mg/m^3 (25 ppm) of C_9-C_{10} aromatics produced lacrimation and/or irritation of the eyes, skin and mucous membranes of experimental subjects. For the C_{11}-C_{12} fraction, the minimum vapor level producing these effects was 104,500 mg/m^3 (19 ppm). Odor detection thresholds were 11,000 mg/m^3 (2 ppm) and 2,500 mg/m^3 (0.5 ppm), respectively, for the C_9-C_{10} and the C_{11}-C_{12} fractions.

There is insufficient data to state that mists of SGF No. 1 would be harmless to humans after acute exposure. The aromatic components of the middle distillate fuels are probably responsible for the noted respiratory tract irritation, whereas the paraffins and cycloparaffins appear to be less noxious.

2. Acute Cutaneous Toxicity

Among industrial workers who were exposed to diesel fuel (details not given) 6 cases of acute dermatitis were observed. The skin reaction occurred about 18 hours following exposure, even though the skin had been thoroughly cleansed. The workers described a feeling of local coolness, followed by burning and pruritis, which continued for as long as several hours (42).

Skin contact with kerosene-contaminated clothing was responsible for a case of epidermal necrolysis, which occurred on the second day of a camping trip in a 12-year-old backpacker who was carrying a fuel container which leaked onto his clothing. The skin eruption involved extensive erythema and detachment of epidermal tissue overlying a purulent exudate (43). This acute chemical burn situation may be equivalent to the industrial setting in which poor personal hygiene practices, such as wearing contaminated work clothes, occur.

Hydrocarbon mixtures boiling in the 177°-316°C range were used in 24-hour skin patch tests. Kerosene caused skin irritation, of varying degrees, in some subjects. A cycloparaffin-rich kerosene fraction in the same boiling range gave more positive skin reactions. The strongest skin irritation response followed patch testing with a highly aromatic hydrocarbon mixture also in the same boiling range. The lower boiling fractions were found to be more irritating to normal skin than higher boiling, oily fractions. The irritation resulted in an eczematous skin reaction (22).

Yaxley (44) presented a case of a diesel fuel injection injury. In the diesel engine, fuel is forced from small jets at a high pressure (6,000 lb/in^2) in a stream of finely divided particles suitable for combustion. An injection tester accidently had diesel fuel forced into the pulp of his index finger. The traumatized finger was numb at first, becoming swollen and painful, with lymphangitis of the dorsal hand. Although the finger was incised for drainage, by the eighth day after the injury, the wound had extended through the terminal phalynx, which became dry and gangrenous by the 22nd day, necessitating amputation. The occurrence of necrosis and gangrene following the subcutaneous tissue trauma and contact with diesel fuel is supported by the fact that small amounts of the substance produced sterile abscesses when injected subcutaneously into rabbit ears, according to the author.

The aromatic hydrocarbons present in middle distillate fuels can produce acute skin changes such as vasodilatation, redness and irritation, when the skin is exposed to them in concentrated form. Short alkyl side groups and branching in the molecules increase their irritant potency.

Aromatic hydrocarbon fractions containing C_9-C_{12} constituents may produce skin lesions severe enough to cause scarring (41). Pure monomethylated naphthalenes, which are found in middle distillates, produce only negative or slight skin reactions in persons undergoing 24-hour patch tests. Gerarde believes that repeated overexposure to monomethylated naphthalenes may result in local irritation of the eyes, mucous membranes and skin. Skin contact with durene, a tetramethylbenzene, causes dehydration and defatting of the skin, leading to dermatitis (8).

3. Acute Gastrointestinal and Pulmonary Toxicity

It has been pointed out that middle distillates may be irritants, and that the aromatic constituents are probably responsible for this effect. Uncomplicated ingestion (without aspiration) will irritate the mucous membranes of the mouth, throat and upper gastrointestinal tract. Lejeune et al. (45) reported a case of a worker who swallowed a quantity of fuel oil (of unspecified composition) during a siphoning operation. The result was an acute gastritis, with epigastric pain and slight hematemesis, which became subacute but persisted for 3 weeks. Early x-rays revealed gastric mucosal lesions and gastric hypermotility. The lesions were completely resolved by 1 1/2 months after the episode, i.e. there were no radiologic sequellae. No systemic involvement was noted.

The danger of ingestion of middle distillate fuels is that aspiration and resultant chemical pneumonitis almost always follow due to coughing or gagging triggered by the fuel. Accidental ingestion of kerosene, as studied by Olsen (46) causes intense irritation of the upper gastrointestinal tract, with immediate vomiting in many cases. Cough, dyspnea and a blood-tinged frothy discharge from the mouth or nose indicate that material has entered the lungs.

There are two mechanisms proposed for the development of pneumonitis (46). The more probable is direct aspiration. The second mechanism is based on the observation that some hydrocarbons which are absorbed from the digestive tract into the bloodstream are excreted through the pulmonary capillaries and exhaled, resulting in the pulmonary irritation.

Szamosi et al. (47) reported 30 cases of diesel fuel ingestion by children under 6 years old. Signs and symptoms included: cough in 13; dyspnea in 3; pneumonia (x-ray evidence) in 25; clinical pneumonia in 10; tachycardia in 19; somnolence in 13; cardiac dilatation in 10; vomiting in 20; fever (38°-39°C) in 15; increased erythrocyte sedimentation rate in 13; and breath and vomitus of characteristic odor in 18 of the 30 cases. Aspiration was chiefly responsible for toxicity and mortality. Pneumonia and fever were frequent in diesel fuel intoxication, in contrast with gasoline, which caused pulmonary edema and death.

Aspiration of diesel fuel in a 44-year-old man caused initial coughing and emesis, followed by marked dyspnea, sinus tachycardia and low-grade fever within a few hours. Progressive infiltration of the right lung lead to cardiorespiratory insufficiency and death after 17 days. Autopsy revealed extensive bilateral pulmonary necrosis and gangrene. Small deposits of Sudan positive (fatty) material were found near the necrotic areas. The severity of the condition may have been due to the quantity of fuel ingested and/or to hypersensitivity from repeated occupational exposure (48).

Liquid aromatic hydrocarbon mixtures cause chemical pneumonitis with pulmonary edema, hemorrhage and necrosis after direct contact with lung tissue in animals. Aspiration of a small quantity causes extensive injury because the low surface tension of the substance enables it to spread over a large area. Liquid alkylbenzenes, alkylnaphthalenes, indanes,

indenes and commercial hydrocarbon mixtures containing these substances will cause similar damage, according to Gerarde (8). It appears that the aromatic components in middle distillate fuels are responsible for the severity of the pulmonary injury after aspiration.

4. Chronic Cutaneous Toxicity

While middle distillate fuels produce dermatitis in some individuals, others who are exposed for years experience no cutaneous toxicity (42).

Repeated contact with diesel fuel leads to constant skin erythema in sensitive individuals. Tense, painful, dry and cracked skin is characteristic and especially marked in skin folds. Eruptions usually contain a purulent exudate (42). In 15 workers, prolonged skin contact caused a slight but gradually progressive dermatitis. Chronic dermatitis led to pyoderma in another 18 cases. Three of the 18 suffered acute dermatitis, characterized by transient hyperemia, edema, vesiculation and sweating of exposed skin, and continued contact caused abscess formation. The pyoderma was usually localized to the face, forearms and back of the hands. Abscess development was favored by hypothermia in cold weather, fever and excessive perspiration. Inadequate personal hygiene was also a contributing factor (42).

A very high percentage of workers in an asbestos-cement factory developed skin lesions, which were attributed to the use of diesel oil as a molding medium. The dermatitis was characterized by folliculitis and furuncles. It would worsen in warm weather, and poor personal hygiene was also a factor in the severity of the condition. The frequency of dermatitis decreased markedly when a paraffin-water emulsion was substituted for diesel oil (49).

Rao (50) noted that industrial fuel oil dermatitis occurred in some individuals after a few months, while in others, resistance continued for years. He investigated the relationship between blood group (ABO system) and occurrence of dermatitis. Twenty-five workers affected with industrial dermatitis were compared with 25 workers who were unaffected after at least 3 years of exposure. The A blood group was evenly distributed between the 2 groups of workers. Two out of 3 persons with B blood developed dermatitis, as did 1 out of 3 with blood group O. There were too few individuals with AB blood to make a similar comparison. Rao concluded that blood grouping provides a rough screening test for the prospective employees to be engaged in work connected with fuel oils during preplacement medical examination.

Diesel engine vapors and exhaust were implicated in a case of a 32-year-old diesel truck driver who developed intermittent follicular dermmatitis (as well as neurologic manifestations). The papular eruption was distributed symmetrically over the inner skin of the arms and legs, skin folds of the axilla and trunk. Histologically, subacute infiltrating inflammation, dermal sclerosis, intracellular vacuolization and epidermal hyperplasia were described. The heavy vapors and exhaust of volatile

hydrocarbons and gas oil contaminated the cabin when ventilation was insufficient, and the skin condition would worsen for example, in cold weather, when the windows of the unheated cabin were closed (51).

Aromatic hydrocarbons in middle distillate fuels cause defatting, drying, scaling and fissuring of skin after chronic exposure. However, skin cancer has not been reported in connection with exposure to middle distillate fuels. The high-boiling polycyclic aromatic hydrocarbons which may be present in blended fuels are inactive, unless refinery procedures have created high concentrations of them in the particular fuel (8, 52).

5. Other Chronic Effects

Laignel-Lavastine et al. (51) reported the development of neurological manifestations in a diesel truck driver. Symptoms included vertigo, staggering, nausea, vomiting, tingling paresthesias, dizziness and headache, persisting for several minutes to a few hours. The symptoms would appear most frequently when the cabin of the truck was poorly ventilated and engine exhaust, containing gas oil, volatile hydrocarbons and carbon monoxide would accumulate. There would be periods of complete freedom from symptoms. Neurological examination revealed no abnormalities. There was a concurrent dermatitis in this case. Evidence is insufficient to implicate diesel fuel as the neurotoxic agent, since the exhaust vapors contained other substances as well.

C. SGF No. 2 Models

SGF No. 2, a lubricating oil, is similar to industrial lubricating oils and their mists. Occupational exposures have received considerable attention in the literature, in studies of respiratory effects, possible carcinogenicity and immunology, among others. The toxicological aspects of the use of medicinal mineral oils, especially concerning mineral oil pneumonia and its relationship to bronchogenic carcinoma, have also been reported in the literature.

1. Acute Toxicity of Lubricating Oil Mist

The irritating ability of fresh motor oil aerosols was investigated in 7 healthy subjects (4 males, 3 females) who sat at rest in a 10 m^3 chamber for 10 minutes, while an aerosol generator dispersed the oil. Mean diameters of oil droplets were 0.2-0.3 μ. Eye irritation, lacrimation, nose and throat sensations were recorded. For mineral oils in concentrations of 10-40 mg/m^3, no appreciable irritation was reported after a 10-minute exposure. This experiment served as a control for evaluating irritants suspended in oil aerosols which occur in smog (40).

2. Chronic Toxicity of Lubricating Oil and Oil Mist

Situations in which chronic exposure to oils and oil mists occurs include the following:

a. Cotton spinning - The lubricating oil used on cotton mule spindles is called spindle oil.

b. Jute spinning - Burlap and sacking are made from jute fibers which are soaked in a mineral oil-water emulsion called batching oil.

c. Newspaper Printing - The printing ink consists of carbon black suspended in mineral oil derived from lubricating oil.

d. Machine Shops - Metalworking requires oils for cooling of parts, cutting operations and machine lubrication.

e. Agriculture - Crops and livestock may be sprayed with mineral oils containing insecticides, pesticides or other chemicals.

Atmospheric concentrations of oil mists in workplaces have been measured, and some findings are presented in Table 7. These concentrations vary from 0.5-402 mg/m^3.

In the majority of metal machining shops in Britain, an oil haze is visible; it can be very intense in the area of certain automatic machines into which continuous bars of metal are fed and shaped into finished products by a series of cutting operations, and which spray cutting oil on the metal being worked (53). The mists are not limited to areas near the machine; general room air of one metal working plant was found to have levels of mist averaging 87 mg/m^3 (54). This author likened the visibility of oil mists to that of cigarette smoke, i.e., the Tyndall effect.

An American plant manufacturing automobile brakes was investigated after complaints of high levels of oil mists had been received (55). The machines were found to splash oil and mists upon workers, as well as on the walkways around the machines, which were slippery with a film of oil. The oil mist concentrations were considered rather dense throughout the facility. Oil mist concentrations of 10-80% of the Maximum Allowable Concentration (MAC) of 5 mg/m^3 were measured, with the average reported as 2 mg/m^3, which is 40% of the MAC (55).

Toolsetters and machine operators are in most intimate contact with the oils and mists, because their work requires constant leaning over the machines (e.g., automatic cutting machine) with subsequent groin contamination if the machine is at this height, as well as contamination of the face, hands, arms if exposed and all clothing that is within spashing range of the particular machine. Even fully automatic machines need to be adjusted and maintained (18, 58, 59, 60).

The oil mists are formed when the oil is vaporized at the high temperature zone of contact between the work and the tool, and then condenses into mist droplets. Automatic screw machines, high speed grinders, thread milling, honing and grinding of razor blades and high speed milling operations including cutting, boring, lathing, milling and wire drawing will all generate oil mists. Intentional spraying of oil may also generate mists, such as for lubrication, and for cooling systems for machinery (61).

TABLE 7.

OIL MIST CONCENTRATIONS IN VARIOUS INDUSTRIAL ENVIRONMENTS

Industry	Measured Concentration in mg/m^3	Reference
Metal machine shop	22-326; average 110 at the operating machine	Grupinski (54)
" " "	8-402; average 87 machine shop room air in general	"
" " "	40-150	Drasche (56)
Screw manufacture	1.0-14.2; 6 observations	Hendricks (57)
Steel manufacture	0.8-50.0; 33 observations	" "
Automobile manufacture	1.0-56.5; 37 observations	" "
Copper mining	5.4-22.0; 7 observations	" "
Newspaper press room	2.0-16.6; 8 observations	" "
" " "	5-21	Goldstein et al. (24)
Brass and aluminum production	1.4-20.7; 5 observations	Hendricks (57)
Automobile brake manufacture	0.5-4; average 2	Hervin & Lucas (55)

There are no known studies which conclusively prove that oil mists are harmless (62). Chronic exposure to industrial oil aerosols has been reviewed in relationship to oil pneumonia, respiratory function studies, dermatitis, oil acne, and cancer of the lung, skin and gastrointestinal tract, and general and cause-specific mortality.

a. Carcinogenicity

Squamous cell carcinoma of the hands, face, and scrotal and vulval skin after chronic exposure to lubricating oils used in metal machinery, cotton and jute spinning has been reported widely in the literature. It usually develops in areas of the body which are exposed to the oils most frequently, and usually is preceded by chronic dermatitis, which is highly prevalent in these workers (19, 20, 53, 59, 60, 63, 64). Because of the interrelationship between dermatitis and skin cancer, these are extensively treated as a unit in the section entitled Cutaneous Toxicity and Skin Cancer.

The possible association between lung cancer and chronic inhalation of industrial oil mists in newspaper printers, metal machinists and other occupationally exposed groups has been examined by many researchers, who have generally concluded that no definite relationship exists between oil exposure and lung cancer (18, 24, 56, 57, 58, 63, 65, 66, 67, 68). The research is reviewed in the section entitled Pulmonary Toxicity and Lung Cancer.

In men with scrotal cancer, the risk of developing a second primary (not metastatic) tumor of the lung, gastrointestinal tract, or skin has been found to be higher than expected for those occupationally exposed to lubricating oils and mists. The phrase "enhanced susceptibility" has been used to explain this finding (18, 53, 63). The details of these epidemiologic studies are presented in the sections dealing with skin, lung, and gastrointestinal tract toxicity.

b. Pulmonary Toxicity and Lung Cancer

Observations of the filtering efficiency of the human nose and on the penetration of droplets and dusts in the lung demonstrate that, in general, particles or droplets greater than 10-15 μ in diameter are filtered out of inspired air by the nose, intermediate size droplets (5-10 μ in diameter) impact in the bronchial tree, and the smallest droplets (under 5 μ in diameter, alone succeed in penetrating to the alveoli. The largest droplets entering the alveoli tend to be retained, while a considerable percentage of those smaller in diameter than 1 μ are exhaled. In other words, the depth of penetration of particles or droplets into the lung increases with decreasing particle size, while the percentage of retention increases with increasing size (69).

Inhalation of mineral oil aerosols generated at industrial workplaces may cause oil pneumonia or paraffinoma (70). Miller 1962 (71) terms the condition "oil aspiration pneumonia" because of its resemblance to the pneumonias produced by swallowing and aspirating medicinal mineral oil.

Industrial oil mist inhalation, even at concentrations over 50 mg/m^3 for many years, has not been attributed to many reported cases of respiratory difficulties. In one investigation of workers exposed for up to 18 years to industrial oil mists in the steel industry, there was no evidence of oil pneumonia, focal pneumonia (paraffinoma), bronchitis or diseases of the nose or throat. X-ray films showed increased linear striations in the lung fields of some of the workers, the importance of which was questionable. Measurements of working conditions revealed oil mist concentrations up to 9 mg/m^3, with 70% of droplets in the 0.8-1.0 μ diameter range (57).

Drasche et al. (56) evaluated by questionnaires the frequency of respiratory complaints (cough, expectoration, dyspnea) in 443 workers chronically exposed to oil-mist concentrations between 40.0 and 150.0 mg/m^3. The oil-mists were derived from drilling and cutting oils used in metal machining operations. There were no signs of respiratory tract irritation due to exposure to the oil mists. However, a protective effect of oil mist exposure against the effects of smoking was significant ($p<0.05$) when compared with a control group of 398 workers of the same age without any occupational exposure to oil mists. (Effects of smoking were not defined).

Goldstein et al. in 1970 (24) studied oil mist occupational exposure in newspaper pressmen. The mists are made up of newspaper ink - a dispersion of carbon black in light grade mineral oil, which is an extract product of lubricating oil. The average droplet size of the mineral oil mist was about 15 μ in diameter, with 15% of droplets in the respirable range (≤5 μ). Air concentrations of oil mist were in the range from 5-21 mg/m^3. Every one of 460 pressmen at one plant who returned to work after an illness diagnosed by his physician as pneumonia, received chest X-rays, and no unresolved pneumonias or oil pneumonia was found on the films. Smoking histories were not obtained. Frequency, severity and disability rates of men with absences from work for respiratory disease for 8 or more days from 1960-1964 were evaluated for the same 460 pressmen and for 700 compositors, who were not occupationally exposed to oil mist. The overall respiratory morbidity showed no evidence for greater frequency of respiratory illness in pressmen, although there was a slightly higher 5-year average severity rate for the pressmen. Analyses of mortality data for 15 years showed no evidence that exposure to oil mist influenced respiratory disease deaths in pressmen. There were 3 pulmonary carcinomas in the pressmen and 6 in the compositors. There were no cases of emphysema among pressmen, and no neoplasms of the nasopharynx or paranasal sinuses in either group.

In a study conducted by the National Institute of Occupational Safety and Health (NIOSH) (55), medical evaluations and interviews of 25 employees at an automobile drum and disc brake manufacturing plant, where mineral oil-water emulsions were used in machinery operations, and oil mist concentrations averaged 2 mg/m^3, revealed that minor respiratory tract infections tended to persist for inordinate periods of time. However, there was no pattern of respiratory tract symptoms which was suggestive of an association with the occupational oil mist exposure.

A cancer mortality study in 5,189 white males who were employed in metal cutting and grinding activities for at least one year between 1938 and 1967, revealed that the mortality patterns for respiratory cancer did not show any exposure-response relationship or latency effect to oil mist exposure. The greatest share of respiratory cancer mortality, in terms of absolute numbers of observed and expected deaths, was contributed by men with less than 5 years of employment. This accounted for the tendency toward an excess of respiratory cancer deaths in the total group of workers. Cause-specific mortality rates for the total U.S. white male population were used to compute expected numbers of deaths. Again, there was no unusual mortality from respiratory cancer among the men exposed to lubricating oil mists (65).

Nickol, 1970 (72) found no clinical or radiographic evidence of respiratory system abnormality in workers in the ball and roller industry in Britain, where high concentrations of oil mist of alveolus-penetrating size are generated by the machinery. From 1950-1964, a total of 492 deaths was reported for male employees and pensioners from a factory employing around 3,000 men. Forty of these deaths (8.15%) were due to bronchial cancer. Bronchial cancer mortality rates for the population of the Borough of Chelmsford and for England and Wales, from 1950-1964, were 6.55% and 6.44%, respectively. No conclusion was offered, due to the fact that the group of workers (including pensioners) was older (not age-matched) than the general population of Chelmsford or of England and Wales.

Respiratory parameters were studied in 77 male and female employees occupationally exposed to spindle oil mists. There were decreases in vital capacity, forced breathing capacity and maximum ventilation of the lungs (observed vs. expected values were compared), which were proportional to the length of employment, being most remarkable in persons employed for 10 or more years. Oxygen consumption and the coefficient of oxygen utilization increased with increasing length of employment. Blood catalase determinations revealed that the activity of this enzyme increased, reaching a maximum at 9-10 years of exposure (employment), and then fell slightly. Bruskin and Kemchenko believed the increased catalase activity and oxygen consumption indicated an enhancement of immunological response to the presence of oil droplets in the respiratory tract, via phagocytosis or other detoxification mechanisms in the lungs. After 10 years of exposure, the defenses were maximally utilized, after which some decline began. It was postulated that the rarity of occupational oil pneumonia is due to the human body's capability of rendering the inhaled oil harmless at such concentrations as are met within industrial exposure. The chronic oil exposure was, however, found to lower immunologic defenses of workers, as evidenced by their higher than expected rate of respiratory illness, especially cold-like diseases (73).

The influence of occupational oil mist exposure upon various respiratory system parameters was analyzed in over 1,700 men who worked in machine shop environments at the time of the study. It was found that age, height, years of cigarette smoking and smoking habits significantly influenced forced vital capacity, one-second forced expiratory volume, cough and phlegm, dyspnea and wheezing, but that years on the job was not a significant predictor for

these parameters. Machine shop oil mist exposure in this experimental group was not associated with an increase in respiratory symptoms or a decrease in respiratory performance (74).

In the same study (74), work histories of all males who died between 1942-1961 were analyzed, and, it was found that 2.9% of the total deaths were due to respiratory system malignancies among oil mist exposed workers. In non-exposed workers at this plant, 3.2% of the total deaths were due to cancers of the respiratory system. It was concluded that oil mist exposure had no adverse effect upon cause-specific (respiratory system) mortality.

According to Falk, 1964, lung cancer in workers exposed to oil mists has been minimal. This might be due to the fact that it is more difficult to diagnose lung cancer than, e.g., skin cancer which has been found to occur with greater frequency in these workers. Also, effective physiologic defenses are at work in the lungs, possibly to prevent initiation of carcinogenic processes (66). The relationship between the development of lung cancer and intake of lubricating oils through inhalation, ingestion or skin contact is unknown (57). Kipling stated that since it has been possible to produce lung tumors in animals by painting mineral oil distillates on the skin of their backs, inhalation of oil mist may not be a necessary condition for producing bronchial tumors. Another reason why oil mist cannot be definitely associated with lung tumors is the lack of documentation of smoking habits among exposed workers (18).

There was one case in the literature in which a 63-year-old man presented with rapidly developing multifocal alveolar carcinoma. Symptoms had included dyspnea and later, bronchiectasis and copious expectoration. Lung X-ray films revealed bilateral infiltrates, resembling bronchopneumonia. This patient had been occupationally exposed to mineral oil mists in a metal machine shop for 23 years. His smoking habits were not reported. The authors attributed the cancer to cutting oil exposure (58).

In 1972, Waterhouse et al. (53) reported that men with cancer of the scrotal epithelium due to occupational exposure to mineral cutting oil mists had an increased incidence of developing another primary tumor (not a metastatis of the scrotal cancer). Second primaries of the skin, upper alimentary tract and respiratory tract were found in 22 of 187 cases of scrotal cancer from 1950-1967, according to the Birmingham, England, Regional Cancer Registry (BRCR). The expected would have been 8.26 out of 187 cases.

Further investigations by Waldron (63) showed that in 288 scrotal cancer cases (all causes) registered at the BRCR between 1936-1971, there were 42 subsequent primary tumors, whereas the expected number would have been 17.11 second primaries — a significant ($p<0.001$) difference. In a subgroup of 162 men occupationally exposed to oil mist, an excess of tumors of the larynx, bronchus, lip, stomach and skin was found. Machine operators and tool setters figured predominantly in the occupations of men with second primaries, together contributing more than half of the cases.

Waldron then studied bronchial and laryngeal cancer cases, categorized by occupation, in men registered in the BRCR between 1967-1969. He reported

that an overall excess of bronchial tumors was noted in men in some oily jobs ($p<0.001$), but not in other oily jobs. Metal furnace workers, smiths and forge workers were represented in the excess of bronchial tumors. There was no excess, however, in laryngeal tumors in this study. The conclusion reached by Waterhouse (53) was:

> If the fact of development of scrotal epithelioma is taken as identifying a population subgroup with evidence either of exposure to mineral oil or of hypersensitivity to mineral oil exposure or both, then the excess of second primary tumors can be taken as an index of the sites most at risk to a malignancy hazard inherent in extended exposure to oil mist.

Waldron further stated that if oil mist is carcinogenic, this effect appears to be exerted only on a subset of the exposed population, possibly composed of persons having an enhanced susceptibility, the basis for which is unclear. Waterhouse felt that assessment of other etiologic agents, such as cigarette smoking and the wide prevalence of both chronic bronchitis and gastric disorders [in England] was necessary.

The basis for the enhanced susceptibility, presumed to be occurring in Waldron's cases, may lie in a constitutional difference in the body's mechanisms of metabolizing lubricating oil components, and specifically, differences in induction of the enzyme aryl hydrocarbon hydroxylase (18). This enzyme, as discussed in the metabolism section of this report, is responsible for microsomal conversions of polycyclic aromatic hydrocarbons into epoxides, which may be carcinogenic. The inducibility of aryl hydrocarbon hydroxylase activity is under genetic control. Persons with a more inducible enzyme might be those with an enhanced susceptibility to tumors from chronic exposure to substances such as lubricating oils and mists (18).

An interesting finding in cases of lipoid pneumonia (due to aspiration of medicinal mineral oil or oily nose drops) is the occasional coexistence of a carcinoma, especially in fibrotic lung tissue. There are no reports of lipoid pneumonia with bronchogenic carcinoma in workers with industrial oil exposure. This lack of evidence may be due to the difficulty in diagnosing this confusing disease entity, or to the rarity of industrial oil pneumonias. The topic will be discussed in greater depth in the section devoted to the toxicity of medicinal mineral oil.

c. Cutaneous Toxicity and Skin Cancer

Lubricating oils used in automatic metal cutting machinery can enter undamaged skin, can penetrate hair follicules, can have a solvent or defatting action, affect the permeability of the skin to other substances, and act as a carrier for bacteria. Oil folliculitis, warts similar to those of cotton spinners, and rodent ulcers and other forms of carcinoma have been observed. Water-oil emulsions ("soluble oils") seem to have the same carcinogenic potency as lubricating oils alone (62). These observations were based on the condition that the offending lubricating oils had not been refined to remove the polycyclic aromatic hydrocarbons which have been found

to be carcinogenic for the skin of humans and experimental animals (23). Refining procedures have been discussed in the Physical & Chemical Properties section of this report.

Oil dermatitis, folliculitis, acne, eczema and contact sensitivity have been found in association with industrial oil and oil mist exposure. In Britain, these skin conditions are classified by the Ministry of Social Security, Productivity and Employment under the heading of PD42. In 1950, PD42 was the commonest prescribed occupational disorder in Britain. Twenty percent of all PD42 was industrial eczema due to exposure to metal cutting oils. Oil acne (folliculitis) affected as many as 80% of automatic metal machine workers (59).

The same author observed that oil acne was very common among workers exposed to lubricating oils alone, but uncommon with exposure to water-oil emulsions. Minor degrees of acne on the arms were found in most workers in large machine shops. The back of the hands, forearms and thighs were most often affected, and scarring was sometimes noted (59).

One medical doctor commented that in his experience in industry, dermatitis, folliculitis, acne and pimples from petroleum distillates could develop in anyone if the length of exposure was sufficient and proper protection and scrupulous cleanliness were lacking (22).

Ankermuller observed 49 cases of oil acne (30 mild and 19 severe) among 245 workers who had been industrially exposed to lubricating, cooling and cutting oils for at least 18 months (75).

In a plant manufacturing automobile drum and disc brakes, medical evaluations and interviews with 25 employees exposed to water-oil emulsion cutting fluids revealed that 10 (40%) of these workers had varying degrees of dermatitis, of which 9 (90%) exhibited oil acne and folliculitis (55).

Jute spinners, who were exposed to batching oils (mostly of mineral oil origin) also were noted to have a high incidence of dermatoses, the nature of which were not elaborated upon (19).

The mechanism by which lubricating oils produce skin disorders has been described as a process of breaking down the skin's protective defenses. According to Hodgson (59), the skin is a barrier defense system varying in thickness and compactness, and being thicker on the palms, thinner on the dorsal hand surfaces, and very thin on the scrotum. Integrity of the barrier depends upon constitutional factors and moisture content. Lipid soluble agents (oils) easily penetrate the barrier, especially the scrotal skin. Inflammations, eczemas, oil acne, and folliculitis only occur when the barrier is passed, but superficial irritation can occur where the oil affects only the barrier. Injury to the barrier, in eczema, after trauma or through loss of moisture, drying and cracking, allows penetration of the oil. It was observed that the amount of oil exposure, the speed of the cutting operations, the flow of oil, and the degree of aerosol contamination all determined the risk of developing oil acne. Friction of clothing contaminated with the oil against the skin was said to increase penetration of oil into hair follicles.

Superficial skin irritation leads, in some cases, to eczema, if lubricant exposure continues. Spindle oil has lead to the development of contact dermatitis on directly exposed skin. Emulsion oils have caused skin irritation and, possibly, very persistant eczemas in persons with dry skin (59).

Oil granulomas of the skin were described as small elevations or ulcers resulting from penetration of oil droplets deeply into the dermis or subcutaneous tissue, due usually to wound trauma (59).

Oil acne and folliculitis result from mechanical blockage of the follicular openings in skin exposed to industrial oils. This results in comedos (blackheads), papules (pimples), and varying degrees of inflammation (55, 60).

Coolant oils may contain microorganisms which can cause rancidity to develop, but these microbes are usually incapable of infecting the human skin (55).

Klauder and Brill (1947, 22) used lubricating oil distillates with boiling ranges above 315°C (spindle oil, neutral oil, transformer oil, and cutting oil) in skin patch tests to determine variations in human skin reactions to these oils. The lubricants generally exerted no irritation when compared with solvents and fuel oils, which were primary cutaneous irritants. Twenty healthy white subjects were tested with a paraffinic light spindle oil, by wetting a 2.5 cm square of gauze with 6 drops of oil and fastening it to the skin for 24 hours. Positive reactions were found in 3 persons (15%), and were classified as mild erythema. In another group of approximately 30 persons who were occupationally exposed to petroleum solvents and had developed dermatitis related to this exposure, paraffinic spindle oil patch tests gave positive skin reactions in 72%. Skin tests were also performed using a cycloparaffinic oil fraction boiling in the lubricating oil range. In 35 white persons with healthy skin, there were 4 (11.4%) positive reactions. In 45 white workers with dermatitis due to occupational exposure to solvents, there were 32 (70.7%) positive reactions. The reactions were mild erythema. In 18 black persons who were not industrially exposed to solvents, there was no reaction to the same cycloparaffinic oil fraction. Twenty whites with eczema (not due to occupational exposure to solvents) were patch tested with this cycloparaffinic fraction, and 11 patients (55%) had mild positive reactions.

The authors concluded that constitutional factors, such as race and the presence of dermatitis, are involved in determining skin reactivity to paraffinic and cycloparaffinic lubricant oils. The individual's tolerance to lubricant oils can be determined by skin patch tests. It was noted that dry or senile skin might be more sensitive than oily skin to the irritant activity of these lubricants, based on the assumption that dry skin cannot rapidly replace the fat which the oil takes out. The increased sensitivity of dry skin to fat solvents was regarded as an anatomic and physiologic skin defect, but not an allergic phenomenon (22).

The prevalence of cutting oil dermatitis in industrial plants in Massachusetts was almost unchanged in 1943 and 1951, although over 1,000 in-

dustrial hygiene bulletins concerning oil dermatitis had been printed and distributed upon request to the industry during these years. Due to this cutting oil dermatitis problem, oils were obtained which fluoresced in ultraviolet light, and could be detected on skin in minute quantities. The fluorescent oils were rubbed onto the forearm (number of subjects not given), then washed off with various hand soaps, sand soaps, corn-meal cleansers, sulfonated oils and several common household detergents. Although the skin of the forearm appeared to be clean after washing, it fluoresced, indicating that oil was still present in the skin after washing. Not one of the 28 tested cleansers removed the oil to the extent that there was no fluorescence.

This unsuspected lack of ability to clean the skin was considered to be an important factor in the development of dermatitis from occupational oil exposure (64).

Oil dermatitis is a possible precursor to skin cancer (60). In prolonged skin exposure to lubricating oils, or in cases where the skin barrier is not intact, dermatitis can progress into chronic degenerative and proliferative changes, due to the direct irritant action of the oil, and the carcinogens and carcinogenic accelerators in the oil. The thin protective barrier of the scrotum, as well as areas of skin soiled by clothing are likely locations for skin cancer to occur. Bare-footed cotton-mill workers used to develop tumors on their feet and legs (59).

Premalignant changes in skin include progressive darkening, net-like discolorations, tendency to sunburn easily, and later chronic atrophic or thickened skin with telangiectasia, labelled as Melanodermatitis toxica in machinists in 1918. Premalignant changes serve as a background for the appearance of benign and malignant skin tumors. The weak oil carcinogens may require 15 or more years for incubation of keratoses (squamous cell carcinomas) (19, 64).

According to Thony et al., 1976 (20) continual contact of skin with liquid lubricants, especially from clothes soiled by leaning over oily machines, and the viscosity of the oils are important factors in carcinogenesis. Exposure of the affected skin to sunlight may also be a contributing factor (59). Cases of skin cancer due to petroleum oils used in industries such as cotton mule spinning and metal manufacture reached a peak in 1928 and declined slowly by 1945, due to the introduction of refining processes--concentrated sulfuric acid washing in the 1930's and later on, solvent extraction--for these industrially used oils. (These processes remove polycyclic aromatic hydrocarbons.) From 1923-1927 in the United Kingdom, there were 361 cases of skin and scrotal cancer in cotton mule spinners, of which 104 were fatal. By 1935, there were 70 more cases, and by 1940, only 40 more cases (66).

The use of refined oils and the decline in mule spinning have reduced skin cancers in the cotton industry, but the annual incidence of scrotal cancer in Birmingham remains the highest in the United Kingdom due to the fact that Birmingham is the engineering industrial center of the country (18).

In machine shops and factories in the United States, Canada, Norway and Sweden, cancer cases due to occupational oil exposure have not been as numerous as in Britain. In Holland, there have been no reports of scrotal cancer among workers exposed to oils, and in Australia the disease is rarely encountered. Kipling offered no explanation for these observed international differences in incidence of scrotal cancer (18).

The Birmingham Regional Cancer Registry reported 298 cases of scrotal cancer from 1936-1972, with a slight upward trend in the number of cases up to 1956, after which time there was a marked increase in the number of cases. Scrotal cancer remained at this high level with periodical fluctuations. Between 1950-1972, Waldron (63) found that 85% of all cases of scrotal cancer could be traced and that 86.2% of these had exposure to oils (47.3% to lubricants only, 2.7% to emulsion oils only, and the remainder exposed to both types of oil). No clear pattern of oil usage emerged because of insufficient data on the sources and composition of oils to which the workers were exposed.

These oil exposed workers with scrotal cancer were found to have significant ($p<0.001$) excesses of second primary tumors of the skin, respiratory tract and digestive tract. Machine operators and tool setters were accountable for over half of the cases of second primaries.

An editorial in the British Medical Journal, 1969, pointed out that between 1920 and 1943 there were no fewer than 1,44[illegible] cases of skin cancer attributable to industrial exposure to mineral oils, and that 855 were scrotal cancers. Scrotal cancers were more frequently fatal than cancers arising on the hands and forearms. A few women workers in the cotton industry had developed cancer of the vulval skin (76).

As of 1950, as many as 60% of workers exposed to liquid cutting lubricants for over 15 years developed chronic inflammatory and cancerous changes on the hands, forearms and scrotum, according to the British Ministry of Social Security, Productivity and Employment records (59).

In 1966, the widow of a man who died from scrotal cancer, which was alleged to have resulted from occupational exposure to certain mineral oils, fought a successful action against a large engineering company, and secured an award of about $20,000 in damages (High Court of Justice, Queen's Bench Division, Birmingham District Registry. Harriet May Stokes versus Guest Keen & Nettlefold (Bolts and Nuts) Ltd., before Mr. Justice Stanwick) (60).

In 650 automated metal industries in one region of France, employing 6,500 persons, 5,000 were exposed to oils by direct skin contact or by aerosols of oil generated in the machines. Cutaneous disorders which were reported from 1960-1974 included 133 cases of squamous cell carcinoma, of which 63% were of the scrotum, 30% were of the arm or hand, and the others were mostly of the face and neck. The scrotal cancer rate for the exposed population of the region was 25 per 100,000, which was 36 times higher than the rate of scrotal cancer in the unexposed population. Risk factors were studied in 3,000 persons, and it was found that psychological, social and

constitutional factors contributed to the risk of developing cancer as well as occupational exposure to oils and degree of personal and occupational hygiene (20).

Hodgson noted that scrotal cancer is a very rare disease. Most men who have been affected in the metal machining, cotton and jute industries were in the 40-50 year age group and had had more than 6 years of oil exposure. In contrast, cancer of the scrotum in non-occupationally exposed men usually occurs after 70 years of age (59).

d. Gastrointestinal Toxicity and Cancer

Occupational exposure to industrial lubricating oils has not been reported as an etiologic agent in disorders of the alimentary tract. In three epidemiologic studies, cancer and mortality rates specific for the digestive organs were briefly examined, and the findings are presented here.

In a cancer mortality study of 5,189 white males who were employed in metal-working industries for at least 1 year, between 1938 and 1967, digestive disease mortality was one category for which the observed numbers of deaths were not too different from expected values (total U.S. white male population). Digestive trac cancer patterns did not suggest any oil exposure-response relationship. For men employed between 10-14 years at metal machining jobs, there were 9 observed deaths, as compared with 5.0 expected deaths. Death rates for specific digestive organ cancers were not examined. The conclusion was offered that digestive cancer mortality was not so different from expected mortality as to indicate any serious health problems (65).

From 1950-1967, there were 187 cases of scrotal epithelioma reported in the Birmingham Regional Cancer Registry. The affected men had increased incidence of developing second primary tumors in general. The upper alimentary tract (larynx) was one site of excessive second primary tumors in these occupationally exposed workers. Due to the wide prevalence of gastric disorders in the general population, however, further study was deemed necessary before conclusions could be presented (53).

In a total of 288 scrotal cancer cases registered at the Birmingham Regional Cancer Registry between 1936-1971, there was a significantly greater ($p<0.001$) number of second primary tumors than expected. Excess of tumors of the lip and stomach were found in a subgroup of 162 men with occupational oil exposure. The details of this study and conclusions have been presented in the section on respiratory cancer. Briefly, it was postulated that because cancer was manifested in only a small subset of the exposed population, unknown factors were responsible for the observed enhanced susceptibility within this group (63).

e. General Mortality

In a 12-year epidemiologic study of oil mist exposure at a newspaper plant, mortality patterns for 778 occupationally exposed pressmen and a non-exposed group of 1,207 compositors were compared. Factors including age,

duration of employment at the plant, study years and causes of death were considered. Significantly higher death rates were found among pressmen first employed at 40 years of age or more, and among men with 20 or more years of employment at this plant, as compared with the compositors. There were no significant differences in death rates for groups first employed at less than 40 years of age (including those working for 20 or more years at this plant). The death rates were 75% (585 out of 778) for pressmen and 53% (634 out of 1,207) for compositors. There were no obvious trends in causes of death of compositors and pressmen. Additional factors, such as previous employment, smoking habits and medical history were not evaluated (77).

f. Other Effects

No information is available on the toxicological effects of exposure to lubricating oils or oil mists on the central nervous system, cardiovascular system, blood or blood forming organs, liver, kidney or urogenital tract.

Studies of the effects on growth, behavior, reproduction, fertility and teratogenesis have not been located in the literature.

3. Toxicity of Medicinal Mineral Oil and Related Formulations

U.S.P. mineral oil, also called liquid petrolatum, has been applied to the human skin (78, 79) ingested as a laxative (71, 80), used in oily nose drops and sprays (46, 71, 81), and employed by the food processing industry (28) as well. This highly refined substance has been found in lungs, liver, lymph nodes and spleens of apparently healthy people with no history of mineral oil ingestion or other use (28). It has been found that ingestion occasionally causes pneumonia both in apparently healthy and in debilitated individuals (46, 57, 68, 71, 79, 81, 82, 83). In some cases of oil pneumonia, the coexistence of carcinoma in the involved lungs has been documented (18, 67, 68).

An examination of the effects of medicinal mineral oil is presented in this section, in an attempt to elucidate possible toxicity of SGF No. 2. It must be kept in mind, however, that U.S.P. mineral oil is a highly refined, non-aromatic extract product of lubricating oil distillates (as discussed in the Physical and Chemical Properties section of this report) and therefore, mineral oil represents only a small part of lubricating oil in its chemical composition. Nevertheless, its physical properties (viscosity and "oilyness") are similar to those of lubricants, and, using this rationale, the effects of the substance on various tissues and organs can be compared.

a. Cutaneous Toxicity

Application of mineral oil to the skin, in baby lotions and other cosmetic products is widespread. Rebello, 1963 (84) found the substance capable of producing acanthosis. His experiment on 15 subjects involved the repeated application of liquid petrolatum to skin previously sensitized to 2,4-dinitrochlorobenzene (DNCB). The subjects (aged 14-70 years) were

sensitized by wearing an occlusive patch containing 2% DNCB in olive oil for 48 hours. Two weeks later, the subjects were tested (challenge) by the closed patch method, to 0.1 ml of 0.1%, 0.05% and 0.01% DNCB, and any erythema, swelling or vesiculation were noted. This procedure was performed on the volar aspect of one arm, and served as a sensitized control.

The other arm was exposed to U.S.P. mineral oil just following the DNCB sensitization procedure and exposure was terminated 24 hours prior to the challenge with DNCB. Exposures were to 0.5 ml of U.S.P. mineral oil twice daily for 2 weeks. Other control skin sites were treated with mineral oil alone. In non-sensitized controls some instances of erythema, vesiculation and papules occurred, but skin challenged with DNCB, as described above, presented much more severe reactions. Spongiosis and vesiculation occurred in one 30-year-old female. The low DNCB challenge concentrations of 0.005% and 0.001% produced only one slight reaction in 12 subjects in control areas, but severe or moderately severe reactions were encountered at these DNCB concentrations in the oil treated areas in 6 out of 12 subjects.

Histologically, the skin reactions could be characterized by acanthosis, hypergranulosis and epidermal and follicular hyperkeratosis, with mild inflammation of the corium, and some instances of spongiosis and vesiculation.

The ability of mineral oil to produce acanthosis was felt to be the basis for the increased reactivity of sensitized skin to a DNCB challenge, caused by mineral oil pretreatment (84).

Although no other human skin sensitivity studies could be located in the literature of mineral oil, animal studies in calves and guinea pigs have confirmed that mineral oil is capable of producing mild hyperkeratosis after repeated application to the skin (85).

Another skin effect of mineral oil is the production of oil acne and folliculitis, due mainly to a blockage of skin pores by the oil. The same condition has been reported after chronic exposure to industrial lubricating oils (55, 59, 75).

Cases of children from a collective agricultural settlement in Israel were reported, in which acne of the face occurred in association with weekly application of paraffin oil to the scalp following shampooing of the hair. In the age group of 2-10 years, approximately 25% of the children (16 boys and 10 girls) were affected at this settlement. The eruption was fairly uniform over the face, consisting of regular groupings of pinhead-sized pimples, with little or no inflammation. The mineral oil was found to have reached the skin of the face and chin indirectly by contamination of the covers of the pillows on which the children slept, the eruption usually being more marked on the side of the face on which the particular individual usually rested. Elimination of the use of this mineral oil brought about the slow disappearance of the oil acne over a period of about 6 months (78).

The author stated that the mechanism of acne production involved clogging of the skin pores with the exogenous oil. The clogged pores, i.e., comedos,

remained as unchanged foreign bodies, with little or no inflammatory response, in the affected children. Unspecified impurities in the oil also might have played a causative role in these cases (78).

b. Gastrointestinal Toxicity

Ingestion of U.S.P. mineral oil as a laxative has led to observations of effects on the digestive system, as well as an opportunity to examine absorption and distribution of the substance. The absorption etc. of mineral oil are discussed in the pharmacokinetics section of this report.

Some conditions for which mineral oil has been frequently used (with or without a physician's advise) are: nasal disorders; perforated ear drum; oral disorders which interfere with the swallowing mechanism; pressure in the throat or neck from tumors, lymphatic enlargement, or goiter; scarring and contracture from tracheotomy or other causes; esophageal diverticulum; esophageal structure; the passage of tubes, instruments or dilators lubricated with mineral oil; cardiospasm with regurgitation and aspiration; tumor or polyp in any part of the gastrointestinal tract; esophagitis, esophageal ulceration or esophageal varices; peptic ulcer with or without pyloric obstruction; spastic colitis, mucous colitis, atonic colon; prostatic hypertrophy or prostatitis; pregnancy, pelvic tumors; hemorrhoids, anal fissure, fistula or stricture; constipating diets, dehydration; neurologic disorders such as cerebrovascular accidents, multiple sclerosis, parkinsonism, especially with loss of gag or cough reflex; cardiovascular diseases such as myocardial infarction, cardiac decompensation, thrombophlebitis (frequently physicians advise mineral oil to prevent straining at stool); and any condition associated with prolonged bed rest and inactivity, such as tuberculosis, fractures, senility or psychoses.

Mineral oil ingestion, for whatever purpose, was once thought to be a dietetic accessory which filtered off toxins, aided in healing lesions of the digestive tract, did not disturb digestion or the digestive organs, was non-absorbable, was excellent for use in surgery and pregnancy and was of high value in treating obesity (80).

Mineral oil ingestion has the following effects on the gastrointestinal tract. It lubricates the sigmoid rectum and creates an abnormal fecal reservoir in the rectum, which normally remains empty until just prior to defecation. Mineral oil and feces remain after evacuation adhering to the rectal mucosa. Mineral oil prevents absorption of fat soluble vitamins A, D, E and K, with resultant problems related to deficiencies of these vitamins (alteration of calcium and phosphorous metabolism through interference with vitamin D absorption; hypoprothrombinemia due to interference with vitamin K absorption). It coats the walls of the intestine and food particles, interfering with absorption of food, and sometimes causing severe weight loss. It may interfere with secretion of bile. It hastens bowel mobility (80).

Side effects occurring with chronic mineral oil ingestion include anal itching, involuntary discharge of oil, flatulence and the possibility of cancer (80).

Dependency may develop to the laxative effects of mineral oil, because it does not correct the cause of constipation. As larger quantities are ingested, the unphysiologic bowel function progressively worsens (80).

Mineral oil is emulsified in the stomach and bowel, and absorbed through the intestinal wall in sufficient quantities to be demonstrable in intestinal lymph nodes, liver, spleen and other tissues (28, 80, 86, 87).

c. Pulmonary Toxicity and Lung Cancer

Mineral oil has been found in the lungs of individuals using oily nose drop formulations (46, 70, 71, 83). A 55-year-old woman was admitted to the hospital with cough, shortness of breath and x-ray evidence of bilateral infiltrates in lung fields, which had already been present for 9 years prior to admission. She had been using oily nose drops for many years. After her death, autopsy specimens of the lungs revealed extensive bilateral lipid pneumonia; the nature of the oily substance in lung sections was determined to be mineral oil by unspecified histologic techniques (46).

In a similar case in a 60-year-old woman with clinical and radiologic signs of chronic bilateral pneumonia, a history of use of oily nose drops was elicited. Sputum lipids were analyzed by thin-layer chromatography, revealing the presence of mineral oil, and confirming a diagnosis of lipoid pneumonia (88).

Mineral oil aspiration apparently occurs in normal individuals, as they regurgitate and aspirate gastric contents during sleep (46). The blandness of mineral oil usually allows it to enter the respiratory tract without causing reflex gagging or coughing (79, 82), although in some cases it has been reported to stimulate this reflex (71). These facts may explain the oil pneumonias occurring in persons known to have taken mineral oil for constipation at bedtime on a chronic basis (46, 71).

However, the infrequency of mineral oil pneumonia in the thousands of individuals taking mineral oil has been emphasized (46, 57, 86). In most cases, the presence of mineral oil in the lungs is asymptomatic, and is an incidental autopsy finding (46, 70, 82). The occurrence of oil pneumonia in infants, debilitated or senile adults and patients with neurologic impairment or pharyngo-esophageal lesions has been noted. A defective swallowing mechanism may predispose to mineral oil aspiration (71).

When mineral oil enters the lungs, the reaction which occurs takes two forms: paraffinoma — a circumscribed lesion within a lobe of the lung, easily mistaken for a tumor; and/or, diffuse pneumonitis — oil droplets widely disseminated throughout one or more lobes of the lung, and possibly accompanied by a bacterial infection (18, 57, 68). The presence of oil in the lungs inhibits ciliary action (71). The lung's response to mineral oil is a foreign body reaction within and around alveoli, with diffuse infiltration of monocytes, eosinophils, plasma cells and giant cells. The reaction serves to eliminate the oil by its expectoration in monocytes, removal by lymphatics and encystment by granulomas. Fibrosis occurs first as thickening of the

alveolar septum, going on to fibrous nodules, some tubercle-like, around collections of oil, and resulting in proliferative pneumonia. This may appear as a circumscribed dense acellular mass, surrounded by a concentric ring of fibrosis with a diameter of several centimeters. The presence of free oil in alveoli is obvious on gross examination. The involved lung tissue may be yellowish or brownish, and oil may be expressed by pressing or scraping with a knife. Microscopically, oil-filled macrophages are found in alveoli, lymphatics and lymph nodes. In some areas, oil collections may extend into the stroma and become surrounded by inflammatory cells and multinucleated giant cells (68, 70, 71, 81, 82, 88).

The pulmonary reaction varies according to the amount of oil aspirated. Dependent portions of the lungs are most commonly involved, and the right lobes more often than the left (79). When small amounts of mineral oil are added to the lung daily, since it cannot be eliminated, accumulation of large deposits in the lungs occurs (68). Oil paraffinomas may put pressure on larger bronchi, produce partial obstruction resulting in bronchiectatic dilatation or produce local inflammation and erosion. Bronchial and bronchiolar inflammation, distortion and plugging with oil have been noted bronchoscopically and bronchographically, and on post-mortem examination (68, 71, 82).

The clinical course of lipoid pneumonia can be entirely asymptomatic; many times the condition is only discovered at autopsy (70, 82). The clinical picture may be a subacute progressive protracted pneumonia, or may be marked by recurrent superimposed bacterial bronchopneumonias, often terminating fatally. More common is an indolent, benign process, clinically resembling a low grade bronchopulmonary infection, being discovered only on routine X-ray examination (70, 71).

When present, clinical symptoms of oil pneumonia are non-specific, and may include dyspnea, cough, wheezing, chest pain, purulent sputum, and hemoptysis (71, 82).

Physical findings, if present, are non-diagnostic. Rales, wheezing, rhonchi, and areas of bronchial breathing and dullness may occur. Signs are usually found at the lung bases (dependent portions), more often on the right side, as in most pulmonary aspiration conditions (71).

Roentgenographic features of oil pneumonia are not characteristic. The picture may be one of unresolved pneumonitis, hilar clouding, a localized density, or widespread fibrosis (linear densities). The lesion is typically unchanging, located at the lung bases, and the X-ray findings are out of proportion to signs and symptoms (71, 79, 82).

In the differential diagnosis of recurrent pulmonary infections, atypical bacterial or viral pneumonias which do not resolve normally, diseases mimicking tuberculosis, chronic bronchitis, bronchiectasis, chronic lung inflammation and tumor, mineral oil aspiration pneumonia must be considered. A careful sputum examination may reveal oil contained in macrophages or free oil droplets, which can be demonstrated by various histologic stains which differentiate mineral oil from animal and vegetable lipids (see Sampling and Analysis section for further details on staining techniques). A past history of mineral oil use is also helpful in diagnosis (71, 81, 88).

The physiologic impairment of the respiratory system in one case of lipoid pneumonia was studied. The subject was a 55-year-old white man with unusually extensive oil pneumonia of 8 years duration. He had ingested mineral oil freely at bedtime for many years, and reported frequently gagging, choking or coughing during ingestion. He felt that mineral oil was beneficial and ameliorated symptoms of an esophageal condition. He experienced malaise, cough, wheezing, hemoptysis and dyspnea. Chest X-ray films showed extensive lung infiltration and a cavity in the left lung. Sputum samples taken 4 days after placement on a fat-free diet revealed oil droplets in macrophages and extracellularly.

The following physiologic findings were reported:

1. Fifty percent decrease in vital capacity and pulmonary compliance, increased residual volume and a 39% increase in the residual volume to total lung capacity ratio.

2. Decreased maximal breathing capacity, increased pulmonary airway resistance, air trapping.

3. Arterial oxygen saturation slightly reduced at rest and markedly reduced on exercise, elevated CO_2 partial pressure, compensated respiratory acidosis.

4. Normal diffusing capacity of the lung for oxygen at rest, increased venous admixture.

The above findings, although suggestive of pulmonary emphysema, were thought to result from fibrosis and broncho-inflammatory reactions to aspirated mineral oil (71).

A case was reported of a 60-year-old woman with a history of repeated episodes of bronchopneumonia. The disease took a fatal course, and it was found at autopsy that chronic cor pulmonale was associated with an extensive lipoid pneumonia from mineral oil aspiration. The cor pulmonale was thought to have come about secondarily, due to the extensive degree of fibrosis and restriction of the pulmonary vasculature. Pulmonary function studies had not been performed, due to the fact that the patient was deaf and uncooperative. Blood gas values had been normal, and polycythemia was not evident, ruling out pulmonary emphysema as a cause of the cor pulmonale (82).

In general, therapy of mineral oil aspiration pneumonia involves discontinuing the use of this substance, correcting any predisposing condition, e.g. swallowing defect, and using supportive measures and antibiotics when indicated. Discontinuation of oil use may lead to a stabilization and possibly a slow resolution of lesions. On the other hand, the lesions may slowly progress through a process of reaspiration of oil set free from disintegrating macrophages which have been coughed up. In symptomatic patients, resection of extensively involved lung tissue has brought about a clearing of symptoms (71).

The relationship between mineral oil aspiration pneumonia and lung cancer is discussed in the section entitled Carcinogenicity.

d. Carcinogenicity

That Dr. Freund, the discoverer of the mineral oil adjuvant combinations, died of multiple myeloma, presumably because of self injections, is often cited by some immunologists (83). However, his disease was diagnosed as early as 1845, while mineral oil came into use only in 1905-1910.

In a review written by Prigal, in 1967, the essence of which is presented below, the carcinogenicity of medicinal mineral oil is refuted.

Mineral oil taken orally is absorbed and found in lymph nodes, spleen and liver, with no evidence of carcinogenicity. Oily nose drops have produced oil pneumonias, but no evidence of carcinogenicity. Mineral oil injected into the pleural cavity in quantities up to one liter, as a treatment for pulmonary tuberculosis, has remained in the pleural cavity for 30 years or more without any carcinogenic activity in thousands of patients. Intra-abdominal instillation of up to one liter of mineral oil for the prevention of adhesions following abdominal surgery, has led to cysts and oil granulomas, chronic inflammation and calcification 20 years later, but no evidence of malignancy. In 18,000 soldiers injected with influenza vaccine emulsified in mineral oil, nine years later there was no increase in incidence of malignancy in the soldiers when compared with suitable controls, and no increased incidence of collagen (auto-immune) disorders. Over a million injections containing mineral oil have been given to humans, and no malignancy at the injection site has ever been reported (83).

Exposure to Fog Oil does not involve injections or instillations into the body and its cavities, but only general body exposure, including inhalation and some ingestion. That medicinal mineral oil, a highly refined and totally saturated hydrocarbon-containing substance extracted from lubricating oil distillates, is seemingly non-carcinogenic -- a fact about which Prigal is thoroughly convinced -- is a moot point in discussing Fog Oil. It must be remembered that SGF No. 2 does contain both aromatic hydrocarbons with some carcinogenic activity, and cocarcinogenic accelerators, as discussed under lubricating oil carcinogenicity. In a few cases of mineral oil aspiration pneumonia, malignant tumors have been found in association with the disease (18, 71).

A 73-year-old woman with esophageal achalasia and chronic mineral oil pneumonia died following surgery for a brain tumor. Lung sections taken at autopsy were microscopically observed to have many mineral oil granulomas and focal fibrosis. In one extensively fibrotic section, several moderately well differentiated adenocarcinoma nodules and some with a more anaplastic pattern were found. Metastasis to the brain and to mediastinal and abdominal lymph nodes had occurred (67).

The possibility exists that cancer arose secondarily in areas of pulmonary fibrosis, rather than direcly from a carcinogenic effect of the oil (18, 67, 68).

In addition, cancer tissue may grossly resemble a paraffinoma, and the association of these two conditions may be overlooked unless many sections of the mass are examined (68).

The rarity of reported cases of concomitant mineral oil pneumonia and lung cancer argues against the carcinogenicity of aspirated medicinal mineral oil in humans. In the same vein, of 11 consecutive adenocarcinomas of the lung from the autopsy and surgical pathology files of one hospital in the USA, no lesion suggestive of mineral oil pneumonia was found (67).

With the above data in mind, Bryan stated that there is no reason to suppose that carcinoma is more likely to develop in a scar induced by mineral oil than in a scar of any other origin (67).

IV. ANIMAL TOXICITY

In this chapter, the discussion of toxic effects of fog oil has been divided into the effects of SGF No. 1, a fuel, and the effects of SGF No. 2, a lubricant. This facilitates the discussion of these two dissimilar fog oils.

A. SGF No. 1

Lushbaugh (89) obtained SGF No. 1 fog oil from the Chemical Warfare Service of the U.S. Armed Forces, and described it as being dark in color and highly fluorescent. His experiments on mice, monkeys, rats and rabbits are the only SGF No. 1 toxicological studies reported in the literature.

1. Mice

Equal numbers of male and female month-old strain A mice, 250 animals total, were exposed for 343 consecutive days to SGF No. 1 oil mists in concentrations of 63 mg/m^3, average droplet diameter about 0.9 μ, in a continuous exposure schedule of 30 minutes of oil mist followed by 30 minutes of room air. At monthly intervals, approximately 6 of each sex were killed. An equal number of unexposed control mice were utilized.

There was histological evidence of oil accumulation in alveolar macrophages, but no lipoid pneumonia or evidence of inflammation was found in mice exposed for 100 days. After 343 days of oil mist exposure, the mediastinal and peribronchial lymph nodes contained a larger proportion of oil than the lungs. A moderate increase in death rate was attributed to the high temperature of the exposure cages (above 90°F) rather than to oil mist inhalation. There were more pulmonary tumors in exposed than unexposed mice, although the tumor-free life was not reduced. The tumors in exposed and unexposed mice did not differ histologically. The tumors in exposed mice bore no spatial relationship to the inhaled oil droplets. The incidence of the lung tumors in control and exposed mice is presented in Table 8.

The small amount of oil inhaled, and its apparent lack of irritating properties in the fine dispersion which was administered may explain the failure of SGF No. 1 to influence the incidence or time of occurrence of pulmonary neoplasms in the strain A mice, which are highly susceptible to carcinogenic influences (89).

2. Rabbits

Four rabbits were exposed for one year to 63 mg/m^3 of SGF No. 1 fog oil, average droplet diameter 0.9 μ, in a continuous exposure schedule of 30 minutes of every hour of every day. No increase in incidence of pneumonia over control animals was noted. Oil was found in microscopic amounts in macrophages in mediastinal lymph nodes and lymphatic channels of the lungs and pleura. No fibroplastic reaction was observed. Histologic examination of the lungs showed few oil containing macrophages in intraalveolar and subpleural locations. None of the rabbits developed pulmonary tumors (89).

TABLE 8.

Incidence of Lung Tumors in Strain A Mice

Exposed for up to 343 Days to SGF No. 1 Fog Oil

Months of Exposure	Exposed Mice				Control Mice			
	Mice	Sex	Av. No. Tumors per Mouse	Range of No. of Tumors per Mouse	Mice	Sex	Av. No. Tumors per Mouse	Range of No. of Tumors per Mouse
1	6	M	0	0	5	M	0	0
	6	F	0	0	5	F	0	0
2	6	M	0.3	0-1	5	M	0.8	0-3
	6	F	1.0	0-2	5	F	0.4	0-2
3	6	M	0.8	0-3	5	M	0.8	0-2
	6	F	0.8	0-2	5	F	0.8	0-2
4	6	M	1.2	0-3	5	M	1.0	0-2
	6	F	0.5	0-2	5	F	1.6	0-4
5	6	M	2.0	0-7	5	M	1.2	0-2
	6	F	0.8	0-2	5	F	0.8	0-3
6	6	M	1.5	0-4	5	M	0.4	0-2
	6	F	2.5	0-8	5	F	2.0	0-5
7	7	M	0.7	0-2	6	M	0.8	0-2
	5	F	3.2	0-11	6	F	2.3	0-7
8	6	M	1.7	1-3	6	M	1.7	0-3
	6	F	3.5	1-6	6	F	3.3	0-10
9	5	M	2.2	0-4	6	M	1.5	1-2
	7	F	3.6	0-9	6	F	2.7	0-6
10	6	M	2.7	2-4	6	M	2.0	0-5
	6	F	4.8	1-7	6	F	1.0	0-2
11	5	M	3.4	1-6	5	M	0.4	0-1
	7	F	2.9	1-6	6	F	2.7	0-7

Ref: Lushbaugh et al. (89)

3. Rats

In 80 albino rats continuously exposed for one year to 63 mg/m^3 of SGF No. 1 fog oil, average droplet diameter 0.9 μ, in a continuous exposure schedule of 30 minutes fog followed by 30 minutes of room air, the toxicological findings were identical to those of the previously discussed rabbits. There was no increase in incidence of pneumonia over control animals, there were no pulmonary tumors, and oil accumulation in the lungs was minimal (89).

4. Monkeys

Seven rhesus monkeys (*Macaca mulatta*) were exposed to SGF No. 1 fog oil, for up to 100 consecutive days. As in the above experiments, the fog concentration was 63 mg/m^3, the average oil droplet diameter was 0.9 μ, and the exposure schedule was 30 minutes of every hour of every day. Five of the monkeys died during exposure, after 44, 67, 71, 77 and 97 days, respectively. Another died 17 days after exposure was terminated, and the last monkey was killed 1 1/2 years later.

Pulmonary oil accumulations were chemically determined. It was found that the amount of accumulated oil was roughly proportional to the length of exposure of the monkeys. The analysis of pulmonary oil accumulation in the monkey killed 1.5 years following the end of the 100 day exposure was lost; no statement of the time required for the oil to be removed from the lung could therefore be made.

Clinical evidence of toxicity, after one month of oil exposure, was shown by the thinning of the fur. By 100 days of exposure, bald areas were observed over more than half of the body surfaces of the monkeys.

There was marked wasting within 30 days, due to decreased food intake, which contributed to the deaths of all exposed monkeys. The stomachs appeared shrunken and fibrotic. Histologically, all but the mucus-secreting cells of the gastric mucosa were atrophic, which was typical of severe hyperplastic gastritis. The gastric mucosa was greatly thickened and ulcerated in many areas. Oil filtered out of nasal passages and swallowed could have caused the severe gastrointestinal irritation (89).

An earlier report of these same monkey experiments focused attention on the finding of gastric adenocarcinomas in the sixth and last monkeys, which was attributed to ingestion of oil contaminating their food and bodies in addition to oil that was breathed and swallowed (90).

The authors recommended that SGF No. 1 should be treated to remove carcinogenic substances, due to the cancer findings reported (90). However, in the subsequent paper in which the same experiment was re-reported (89), the authors stated that chromatographic analyses of SGF No. 1 indicated the absence of any carcinogenic compounds, and they further made no mention of the gastric carcinomas, referring instead to a phenomenon of infiltration of mucosal cells into the submucosal connective tissue in a carcinoma-like fashion. Because of the fact that the two reports of the same experiment are contra-

dictory, no conclusions can be drawn as to the possible carcinogenic activity of SGF No. 1 fog oil for the gastrointestinal tract of monkeys.

The pulmonary oil accumulation in the 7 monkeys was described histologically as focal pneumonia with interstitial inflammation. Oil-containing macrophages were found thinly scattered throughout the alveoli, and later were present in the lymphatics of the lung tissue. Oil contained in macrophages was present in both fine and large droplets. Longer exposures led to increased numbers of fibroblasts and connective tissue in the lipophage containing areas, and the formation of condensed fibrotic nodules containing oil.

Monkey 1, which died after 44 days of exposure, had diffuse pneumonitis. Monkey 2 had a less extensive pneumonitis than monkey 1, after its death at 67 days of exposure. The third monkey, which died after 71 days of exposure, had twice the number of pulmonary oil macrophages as Monkey 2. Alveoli were occasionally filled with clumped oil-containing macrophages. These cells were also increased in perivascular tissue and lymphatic channels. Some areas of the lungs were filled with a proteinaceous exudate containing lymphocytes. Monkey 4 died after 77 days of exposure. The lungs of this animal were similar, except for the exudate, to those of Monkey 3. Monkey 5, dead after 97 days of exposure, had intra-alveolar clumps of oil-containing macrophages. Fibroplastic reactions were developing in lymphatic channels and connective tissue areas. Monkey 6, which died 17 days after termination of the 100-day exposure, had only rare alveolar macrophages. Almost all lipophages were in the lymphatic channels and perivascular connective tissue. The monkey killed 1.5 years after the exposure had small amounts of oil in lymph nodes and lymphatic channels of the lungs where small fibroplastic nodules were present. Clinically, the monkey had remained well.

It was further stated that the incidence of infectious pneumonia in monkeys exposed to oil fogs was greatly increased in comparison with other unexposed monkeys (89).

B. SGF No. 1 Models

The toxicity of diesel fuel, deodorized kerosene and alkyl aromatic compounds has been studied in various animal experiments, including inhalation of mists and vapors, ingestion, aspiration and percutaneous application.

1. Toxicity of Mists and Vapors

Rats, rabbits, mice, dogs, monkeys, cats and guinea pigs have been exposed to mists of middle distillate fuels and some concentrates of individual hydrocarbons which are found in these fuels. The literature is presented as follows:

a. Rats

The effect of diesel fuel on the surfactant layer of the lung was investigated in Wistar rats weighing 175 to 300 g. The animals were placed in a 12-l chamber into which diesel fuel, vaporized on a hot plate at 400°C

and then cooled, was introduced in aerosol concentrations up to 10,000 mg/m^3. Droplet size averaged less than 2 microns in diameter. The duration of exposure and temperature of the chamber were varied in an unspecified manner. Inhalation did not damage the pulmonary surfactant layer, as demonstrated by pressure-volume lung deflation curves (hysteresis) at low transpulmonary pressures. When kerosene was substituted for diesel fuel, under the same conditions, the pulmonary effects were equally negative (14).

Deodorized kerosene vapor inhalation was investigated by Carpenter et al. (7). Six male albino rats weighing 90-120 g were placed in an atmospheric chamber saturated with kerosene vapors for 8 hours. They were then observed for 14 days and sacrificed. The rats remained normal in appearance and weight gain and there were no remarkable autopsy findings. Tests were performed on 6 male albino rats inhaling deodorized kerosene aerosols with droplet size averaging under 1 micron in diameter, in which the rats inhaled concentrations of 6900 - 9600 mg/m^3 for 6 hours on 4 successive days. On the first day of exposure, loss of coordination and sluggishness occurred, and following the second exposure day, there was redness of the extremities. After the 4th day of exposure and an additional day of rest, the skin of the extremities was dry and flaking, and remained in this condition for 4 days following exposure. One of the 6 had slight hair loss. Body weight remained normal during and up to 14 days following the exposure.

Carpenter et al. also investigated the subacute inhalation toxicity of deodorized kerosene, monitoring body weight change and blood and urine analyses in male rats (26). A group of 25 rats was exposed to an aerosol concentration of 100 mg/m^3 for 6 hr/day, 5 days/wk, for 13 weeks. There were also 25 unexposed rats. One rat died of pneumonia after 30 days. No weight loss had been noted. Mean urine pH was significantly higher ($P < 0.05$) and specific gravity lower than controls after 8 weeks of exposure but both had returned to normal values by 13 weeks. One rat which was killed after 8 weeks of exposure had a significantly elevated serum alkaline phosphatase activity, related to the pleural adhesions and abscess bronchopneumonia noted on autopsy. The other rats developed no abnormalities considered to be related to exposure. There were no other statistically significant deviations from the control group in any of the monitored criteria. Of 25 rats exposed to 50 mg/m^3 of deodorized kerosene aerosol in the same schedule as above, one rat lost 40 g of weight in 7 days and died after 16 days of exposure, due to bronchopneumonia. In the other rats, the mean erythrocyte count was slightly depressed at 8 weeks, although still within normal limits, returning to control levels by 13 weeks. Histopathological reports of lesions did not differ either in type or frequency for exposed compared to control rats. Sporadic findings of slight tubular regeneration of the kidneys were not considered to be treatment-related. Carpenter et al. concluded that these subacute exposures did not produce progressive dosage-related effects which could be considered adverse effects caused by the treatment.

In contrast to studies with diesel fuel and deodorized kerosene (which contained <3.9% aromatics), where minimal effects were produced from aerosol or vapor inhalation, animals inhaling aromatic hydrocarbon distillates in the lower end of the diesel fuel boiling range suffered severe damage. Nau et al. (41) studied the C_9-C_{12} fractions, containing alkylbenzenes, naphthalenes, indanes, cycloparaffins and paraffins (see Table 9) in rats, using the following criteria to detect changes from normal: appearance, behavior,

weight gain, organ weights, hematological findings, bone marrow changes and gross and histopathologic changes. Laboratory rats exposed to 5200 mg/m^3 of C_9-C_{10} vapors for 18 hours every day developed lung and liver congestion, enlarged spleens and hemorrhagic kidneys at the end of one day of exposure. By the 8th day, the total white blood cell count was significantly lowered, with increased neutrophil and decreased lymphocyte counts. Expected weight gains did not occur, and there was increased transparency and fragility of the femurs. When rats were exposed to 3200 mg/m^3 of C_9-C_{10} vapors, under the same conditions for as long as 2,424 hours there was significantly lower weight gain and a significant ($p<0.05$) fall in the total white blood cell count. Congestion and hemorrhages were present in the lungs, liver, kidneys, spleen and omentum after a few days of exposure. After 54 hours of exposure, there were focal inflammatory changes in the lungs and fatty livers. After 400 hours, there were hemorrhages around the nose and mouth. Bilateral cataracts developed in 70% of rats which were set aside for 2 months with no additional exposure, where none of the controls developed cataracts. Eye changes included focal accumulations of enlarged epithelial cells with vacuolated cytoplasm, areas of fibroblastic proliferation but no inflammatory cells. There were no significant changes in organ weight. Numbers of myelocytic precursors in the bone marrow were increased.

Rats exposed to 3200 mg/m^3 of vapors of C_9-C_{10} alkyl aromatics for 23.5 hr/day for 7 days developed hemorrhages of the kidneys, omentum and subcutaneous tissue. Rats exposed continuously to 3200 mg/m^3 for 24, 36, 54 or 72 hours showed transitory blood changes only, whereas no changes occurred in rats exposed to 3200 mg/m^3 for 18 hours per day, every other day (total of 3 exposures) and then set aside for observation for 9 months. Lower concentrations (1000 and 260 mg/m^3) produced no changes in rats after more than 700 hours of exposure for 8 hours a day, 5 days a week.

TABLE 9

Alkyl Aromatic Composition of Fractions Used Experimentally by Nau et al. (41).

Components	C_9-C_{10} Fraction BP:155-200°C	C_{11}-C_{12} Fraction BP:200-249°C
Paraffins	20 mol %	6 mol %
Cycloparaffins	6 mol %	0 mol %
Alkylbenzenes	74 mol %	44 mol %
Indans	0 mol %	27 mol %
Naphthalenes	0 mol %	23 mol %*
Tricyclics	0 mol %	0 mol %
Alkylbenzenes		
C_9	42 mol %	7 mol %
C_{10}	29 mol %	10 mol %
C_{11}	3 mol %	24 mol %
C_{12}	0 mol %	5 mol %
C_{13}	0 mol %	1 mol %

*13.5 mol % naphthalene; 9.5 mol % 2-methyl naphthalene

Rats inhaling 3200 mg/m^3 of C_{11}-C_{12} alkyl aromatic vapors, for 18 hours every day did poorly; 50% of 37 animals died after one 18-hour period. There was severe weight loss, engorgement of all organs with blood, small spleen, and liquid and gaseous material filling the intestines. Exposures for 8 hours every day caused rapid deterioration and weight loss after 15 days. Autopsy findings included small spleen, hemorrhagic lungs and liver and bloody and gaseous intestinal contents. Exposures for 5 hours a day caused hair coarsening, emaciation and vesicles around the eyes, nose and feet, marked decrease in the total white blood cell count, with increased neutrophil and decreased lymphocyte counts, possible CNS depression and low rates of weight gain. Femoral softening and "watery" bone marrow were observed when these rats were exposed for up to 1,683 hours. There were no cataracts. Good recovery occurred over 4 months following the end of the experiment.

Rats exposed to 1280 mg/m^3 of C_{11}-C_{12} vapors for 8 hours a day, 5 days a week (90 exposures) showed a fall in white blood cell count and a slower weight gain than expected. One of the 17 rats developed a cataract. Bone marrow revealed an increase in erythrocyte precursors and a delayed decrease in the proportion of myelocyte precursors. Rats exposed to 320 mg/m^3 (same schedule) showed slight slowing of expected weight gain, and the same bone marrow changes as rats exposed to 1280 mg/m^3.

Acute LC_{50} values for the alkyl aromatics (41) in 150 g rats were 14400 mg/m^3 of C_9-C_{10} for 7 hours, and 4600 mg/m^3 for C_{11}-C_{12} for 7 hours. In the latter case, 4 out of 10 rats died within 96 hours following exposure, whereas with the lower-boiling fraction, 4 out of 10 died after 7 hours of exposure.

In rats receiving 27 daily one-hour exposures to methylated naphthalene solvent mist (an aromatic hydrocarbon), at a concentration of 2830 mg/m^3, median droplet size of 3.15 microns, there were no deaths, no weight losses, and no abnormal hematological findings (8).

b. Rabbits

In groups of rabbits intermittently exposed to diesel fumes, Samal et al. (91) found alterations in immunologic response. Animals were exposed for 2 hours each day for 80 days to smoke from a mixture of diesel and motor oil (100:6). Subcutaneous injections of typhoid-paratyphoid vaccine were given on day 0 (0.5 ml) and on day 50 (1.0 ml), and antibody titers were estimated by the Widal test (flocculation and precipitation), before exposure, and then every 10 days throughout the experiment. The exposed rabbits generated less antibody to the vaccine than controls. In the controls, immune titers showed an initial rise, levelled off at day 40 and fell after day 70, while in the experimental animals there was a steady increase in immune titer for 70 days, indicating absence of the secondary response. Other possible effects of inhalation of the fumes were not discussed.

Rabbits inhaling methylated naphthalene solvent mist (an aromatic hydrocarbon) at a concentration of 2830 mg/m^3, median droplet size of 3.15 microns, for one hour each day for 27 days developed redness of the ears

after the 4th exposure. There were no hematological abnormalities and no deaths. Moderate liver fat deposition and slight epithelial hyperkeratosis of the ears were the only pathological findings (8).

c. Mice

Mouse respiratory rates were not affected by high kerosene vapor concentrations (7). Six mice exposed to 6900 mg/m^3 of deodorized kerosene aerosol developed a slightly depressed breathing rate. There was no respiratory tract irritation from exposure to saturated vapors at room temperature or from 6900 mg/m^3 aerosol (duration not given).

Mice exposed to 2830 mg/m^3 of methylated naphthalene solvent mist for one hour daily for 27 days developed dyspnea, restlessness, prostration, irritation of eyes and redness of ears after the second hour of exposure, and slight weight loss occurred. Hematologic studies were normal. Eight out of 20 died; the majority of these deaths occurred during the first three days of the experiment. Autopsy findings included bronchopneumonia, parabronchial alveolar septal thickening, edema and emphysema (8).

Nau et al. (41) determined acute inhalation LC_{50} values for C_9-C_{12} alkyl aromatic hydrocarbons in 27-gram CFW mice. The vapor concentrations were 9700 and 3400 mg/m^3 for 3 3/4 hours for C_9-C_{10} and C_{11}-C_{12}, respectively.

d. Rhesus monkeys

Nau et al. (41) studied the effect of vapors of C_9-C_{10} alkyl aromatic hydrocarbons on Rhesus monkeys. Three monkeys, weighing 1.8 kg, inhaled 1000 mg/m^3 for 7 hours a day, 5 days a week for 90 exposures. They appeared groggy or sedated during exposures. Tremor developed during the first week, and then diminished throughout the experiment. White blood cell counts decreased, with increased neutrophil and decreased lymphocyte counts. There was hair loss and dry leathery skin, but no gross or microscopic changes other than a slight decrease in erythrocytic and myelocytic precursors in the bone marrow. Monkeys inhaling 260 mg/m^3 under the same exposure schedule for 90 exposures showed no changes except an elevated hematocrit and peripheral white blood cell changes similar to those in the above-mentioned monkeys.

Four Rhesus monkeys exposed to 1280 mg/m^3 of vapors of C_{11}-C_{12} alkyl aromatics for 7 hours a day, 5 days a week (90 exposures) developed eye and facial irritation, diarrhea after 2 days, neutrophilia and lymphocytopenia of peripheral blood, and increased erythrocytic and decreased myelocytic precursors in the bone marrow. At vapor concentrations of 300 mg/m^3 (same exposure schedule) monkeys developed diarrhea by the third day and the same changes as the monkeys exposed to 1280 mg/m^3.

e. Dogs

The subacute inhalation toxicity of deodorized kerosene was investigated in male beagles (7). Body weight, blood and urine parameters were monitored. No adverse effects were noted with the 13-week inhalation of 100 mg/m^3 for 6 hours a day, 5 days a week. There was a slight elevation

of polymorphonuclear leukocytes. Beagles exposed to 20 mg/m^3 of deodorized kerosene aerosol showed a borderline but significant ($p<0.5$) mean weight increase after 13 weeks. There were no treatment-related histopathologic findings.

Dogs exposed to 2830 mg/m^3 of methylated naphthalene mist for one hour a day developed marked salivation after the 4th day of exposure. There were no abnormal hematological findings and no deaths (8).

f. Cats

Deodorized kerosene aerosol concentrations of 6400 mg/m^3 produced no signs of neurotoxicity during the 6-hour exposure, and no alterations in weight gain for 14 days following the exposure, in 4 male cats of mixed breed (7). No treatment-related abnormalities were revealed at the autopsies performed 14 days after exposure.

g. Guinea pigs

Six male guinea pigs were exposed to methylated naphthalene solvent mist, in a concentration of 2830 mg/m^3, median droplet size 3.15 microns, for one hour a day for 27 days. Dyspnea occurred following each exposure. There were no weight losses or hematological abnormalities. One animal died around the 10th day of exposure, with pulmonary edema evident at autopsy (8).

2. Ingestion and Aspiration Toxicity

Ingestion of middle distillate fuels by farm or laboratory animals may lead to changes in blood chemistry and hematologic picture, as well as gastrointestinal tract involvement. If fuel is aspirated into the lungs, pulmonary damage results. Findings in rats, rabbits, and farm animals are reported.

a. Rats

Diesel fuel was said to have a low toxicity in rats, in a study performed by Starek et al. (92). In 138 Wistar rats, weighing 180-340 g, given diesel oil by stomach tube, an oral LD_{50} of 16.0 ml/kg of body weight (range of 6.7-38.4 ml/kg) was established. The peripheral blood picture in rats fed 20 and 25 ml/kg/day revealed a significant drop in hemoglobin after 14 days, significant reticulocytosis after 7 and 14 days, elevations of neutrophilic granulocytes after 7 days and reduced lymphocytes and thrombocytes. Erythrocyte counts were normal. Elevated serum enzyme levels of malate dehydrogenase, aspartate aminotransferase and alanine aminotransferase were found, but alkaline phosphatase levels remained normal. The subacute lethal dose of diesel fuel in rats was calculated to be 43.2% of the acute LD_{50}, i.e. 6.9 ml/kg of body weight per day, based on observations in 5 rats orally administered increasing daily dosages from 0.06-10.8 ml/kg of body weight over a 32-day period. Three died when the dose reached 3.2 ml/kg on day 18; the other 2 died when the dose reached 10.8 ml/kg on day 32.

Wistar rats weighing 175-300 g were given 2.0-3.0 ml of kerosene by direct instillation into the duodenum. In the 9 experiments, there were no changes in lung stability 18 to 24 hours later as measured by pressure-

volume determinations of deflation under low transpulmonary pressure (hysteresis) (14). No other parameters were studied. This experiment showed that ingestion without aspiration of kerosene was incapable of causing respiratory toxicity.

Entry of middle distillate fuels into the lungs will cause pulmonary damage and signs of respiratory distress. Wistar rats weighing 175-300 g were subjected to instillation of 0.01-0.10 ml of diesel fuel into the trachea via a cannula. The animals which were killed 15 minutes later showed significant, dose dependent differences in pulmonary stability (hysteresis), indicating damage to the surfactant layer. An intratracheal dose of 0.05 ml of diesel fuel produced 50% mortality. In animals remaining alive, lung stability increased and returned to normal level levels after 48 hours. In another group of rats given 0.1 ml/kg body weight, after 14 days the lungs were macroscopically normal, although microscopically there were small patches of resolving pneumonia. When kerosene or mineral seal oil (boiling range 196-292°C; 76.6% paraffinic, 1.4% olefinic, 22% aromatic) were instilled into the trachea in the same experimental setup, the pulmonary effects were indistinguishable from those of diesel fuel. The ability of diesel fuel and similar oils to damage the lung lining was proportional to the quantity which was introduced into the trachea, but was not influenced by the relative proportions of aromatic and paraffinic hydrocarbons in the oils tested (14).

Gerarde (93) studied diesel oil aspiration in 2 male albino Wistar rats weighing 300-400 g. The animals were given 0.02 ml (a mouthful) while apneic, and the material was aspirated when the animals regained their ability to breathe. This dose was lethal in 24 hours for 2/2 rats. Pulmonary findings were characteristic of acute chemical pneumonitis: severe pulmonary edema, hemorrhage, and liver-like appearance. Clinically, the animals developed tachypnea, dyspnea, cyanosis, and a blood-tinged frothy nasal discharge. In a discussion of related hydrocarbon mixtures, Gerarde (8) reported that rats aspirating 0.2 ml of kerosene also developed acute chemical pneumonitis. Liquid alkylbenzenes, alkylnaphthalenes, indanes, indenes and commercial hydrocarbon mixtures containing these substances also damaged the lungs when aspirated.

b. Rabbits

Ten rabbits, weighing around 2.5 kg were fed 1 ml/kg body weight of a fuel oil having a boiling range of 150°-300°C. Blood sugar levels were determined after 30 minutes, 2, 5, 7, 9 and 12 hours. There was a gradual drop in blood sugar, reaching minimum values (as low as 23% below normal) between 5 and 7 hours, and returning to control levels by 12 hours. Petroleum derivatives boiling in slightly lower ranges caused similar changes (94).

After observing a patient with fatal pulmonary gangrene following diesel fuel aspiration, Haraszti (48) was able to reproduce the pathologic effects in the laboratory. In rabbits, 6-8 days following intratracheal administration of 1 ml of diesel fuel, pulmonary changes of progressive interstitial infiltration (hypermia, capillary endothelial damage, edema, alveolar hemorrhage or exudation and bronchiolar necrosis) were noted.

c. Farm animals

Two veterinary reports of poisoning, in a cow and an ewe, are presented, because the clinical findings are indicative of systemic toxicity. The amount of fuel ingested could only be approximated in these cases.

The ingestion of up to 7 liters of diesel fuel by a cow lead to slight fever (39.5°C), reduced heart rate, palpitations, reduction in appetite and slowing of peristalsis in the first stomach. This was followed by mild diarrhea, then constipation, a considerable decrease in milk production and a stiff and uncertain gait suggestive of muscular weakness. Painful swelling of the hind fetlocks occurred 5 days after the poisoning. The animal slowly recuperated with treatment after the 8th day (95).

Ranger (96) reported a case of poisoning in an ewe after the consumption of diesel fuel-soaked grass. The animal was depressed, weak, had lost weight, and had a strong odor of diesel fuel emanating from the breath, urine and feces. Slight dyspnea, respiratory signs and increased rumenal peristalsis were also reported. After 10 days without improvement, the contents of the rumen were removed and replaced. The rumenal wall contained an area with raised nodular lesions up to 3 cm in diameter, with ulcerating caseous centers. Following rumenotomy, the animal recovered, although complete loss of fleece occurred. Hematological changes included neutrophilic leukocytosis and moderate normochromic anemia, but there were no changes in serum concentrations of liver enzymes.

3. Cutaneous Toxicity

Sensitization, primary irritant activity, skin painting experiments in various species, and dermal implantation are reviewed.

a. Sensitization in guinea pigs

Negative results were reported following sensitization studies with diesel fuel in 24 white male guinea pigs, weighing about 400 g. The Landsteiner and Jacobs technique was utilized (97).

b. Primary irritation in rabbits

Diesel fuel was classified as a mild primary irritant to the skin and conjunctiva of the eye of 10 white Belgian rabbits weighing 3500 g. The Draize et al. method was employed (97).

c. Percutaneous toxicity

Skin painting experiments with rats, rabbits, guinea pigs and mice are presented.

(1). rats

In male Wistar rats weighing around 250 g, undiluted diesel oil was applied to the skin of the tail for 6 hours each day for 10 days. Epidermal

splitting and exfoliation, hair loss, and a papular rash occurred, and generally receded 2-3 weeks after termination of exposure (97). There was no mortality or significant weight loss. Blood studies did reveal decreased hemoglobin concentrations (11% below normal on the 17th day of the experiment). The red blood cell count was decreased by 13% on day 17, 24 and 31. The elevated reticulocyte count, mean 58% above normal, was significant ($p<0.05$) on day 17. The leukocyte count was up by 61% on the 11th and 17th day. Neutrophilic granulocytes increased by 175%, which was statistically significant ($p<0.05$) on day 11, 17 and 24. There were no changes in thrombocytes or lymphocyte counts. Blood serum chemistry revealed increases in aspartate aminotransferase and the intermediate lactate dehydrogenase (LDH) isoenzymes, and decreased activity of heart and liver (muscle) fractions of lactic dehydrogenase. The authors concluded that absorption of diesel fuel through the skin caused a direct effect on blood-forming organs, leading to decreased production of red blood cells and stimulation of reticulocyte formation, neutrophilia and lymphocytopenia. LDH isoenzyme changes may have been secondary to cell damage of the myocardium, erythrocytes and hepatocytes.

Starek and Cembala (98) investigated the skin effects of Mentor 28, a substance used in the electroerosive industry. This hydrocarbon mixture distills in the range of 278°-320°C; its composition is 77.0% paraffinic and cycloparaffinic, 19.9% aromatic and 3.1% olefinic. When applied to the tail skin of Wistar rats for 6 hours a day for 10 consecutive days, splitting, exfoliation of epidermis, hair loss and nodular exanthema resulted. Cosmetic naphtha (99% paraffinic) and turbine oil produced less severe skin changes, leading the authors to conclude that the higher aromaticity of Mentor 28 was responsible for its greater activity. When Starek et al. (97) compared the skin effects of Mentor 28 with those of diesel fuel, using identical tail painting schedules, the rats' skin reactions were similar in both experiments, consisting of epidermal splitting and exfoliation, hair loss and nodular exanthema.

(2). guinea pigs

Skin compatability to diesel fuel was tested in 5 albino guinea pigs weighing 270-550 g. The substance was applied to the shaven skin of the back 5 times a week until a skin reaction appeared. By the 5th day, there was slight erythema, followed by desquamation, induration, hair loss and rhagades while treatment continued. The experiment was stopped on day 19 due to increasing restlessness of the animals as well as to advancing skin ulceration and intensified crusting which had first been noted on the 12th day. Recovery was rapid, with the skin healing in 10 days and new hair growth in 15 days (99).

Hoekstra and Phillips (85) studied the effects of various petroleum fractions on the skin of male albino guinea pigs weighing 300-500 g. Applications were made every other day for a total of 4 exposures, and the animals were observed for 20 days following the first application. The oils were characterized as aromatic-rich, paraffin-rich and cycloparaffin-rich fractions. All fractions produced hyperplasia, hyperkeratosis and hair loss, but the aromatic and isoparaffinic fractions were more potent than the paraffinic and cycloparaffinic fractions. In addition,

the higher boiling fractions were less noxious than lower-boiling ones. The transition from non-damaging to noxious was abrupt, occurring in the range of 350 ± 15°C. Aliphatic fractions boiling above 350°C (21-23 carbon atoms) were protective when mixed with the noxious fractions, i.e., the mixture caused less skin reaction than the low-boiling fraction alone. Fractions with 14-19 carbon atoms caused the most severe reactions. The aromatic hydrocarbons were skin damaging even at the highest boiling point studied (402°C), unlike the aliphatics.

(3). mice

C_9-C_{12} alkyl aromatic hydrocarbons boiling in the middle distillate range were applied to the skin of 79 male C_3H mice, in doses of 0.10-0.15 g, 3 times a week for 150 applications. Skin became thick, dry and scaly, and there was evidence of hyperkeratosis in 31%, epidermal atrophy in 24%, inflammatory reaction in 41%, perikeratosis in 23% and ulceration in 25% of the group. The C_{11}-C_{12} fraction, applied to 85 mice, also resulted in thick, dry and scaly skin, and hyperkeratosis in 30%, perikeratosis in 16%, epidermal atrophy in 29%, inflammation in 23% and ulceration in 6% (41).

In a report by Twort and Twort (100) in which various catalytically cracked oils were topically applied to mice in a search for carcinogens, they also observed that "lighter grade diesel fuel oils are non-carcinogenic for the skins of mice, but a heavier grade tested was definitely carcinogenic". When lighter grade oils having very low viscosity and the appearance of colored kerosene were applied daily to the interscapular region of 100 mice, only dermatitis was observed. The heavier grade diesel fuel oil, described as an older type dirty-looking oily mixture with a high viscosity, induced 18 tumors in 100 mice after daily application; three of the 18 tumors became malignant. With two applications per week in another 100 mice, only one tumor was observed.

According to Fisher et al. (52) and Gerarde (8), only very high-boiling petroleum products display appreciable carcinogenicity in mice. The carcinogenic constituents occur in distillates boiling over 370°C, and are associated only with the aromatic fraction, and especially with the polynuclear aromatics. Heating oils and related products which are lower-boiling are not carcinogenic, even when they are partly aromatic. Many high-boiling products are also inactive, unless the creation of highly condensed aromatic hydrocarbons occurs in their synthesis or processing.

In generating SGF No. 1 oil smoke, thermal decomposition or cracking may occur when the oil or oil mist contacts heated parts of the smoke generator. However, there is no documentation either on the extent of cracking or on the thermal decomposition products which could result. (See the section entitled Generation of Smoke, in the Physical and Chemical Properties chapter of this monograph.)

d. Dermal implant in rats

The effect of diesel oil on formation of granulation tissue in Wistar

rats, weighing 100-170 g was investigated by Bien and Buntrock (99). Plastic rings were implanted in the dorsal skin of the rats, the liquid was added and left in contact for 10 days, and then the granulation tissue formed was removed, examined histologically, and analyzed for hydroxyproline content and ratio of moist to dry weight. The diesel fuel promoted formation of granulation tissue in a dose dependent manner, giving higher dry tissue weight than control substances, but there was no significant difference in amount of hydroxyproline between diesel fuel-treated and control tissues.

G. SGF No. 2 Models

Investigations of the toxicity of SGF No. 2 have not been reported in the literature.

Animal toxicologists testing lubricating oils and medicinal (highly-refined, white, non-aromatic) mineral oil have most often performed skin painting experiments in various species, looking for evidence of carcinogenicity or the ability to promote cancers. Other investigators have subjected animals to acute or chronic exposures to aerosols of the oils, studying systemic effects such as the occurrence of lipoid pneumonia, immunological suppression, renal, myocardial and hepatic degenerative changes, or lung tumor acceleration and/or inhibition in tumor-susceptible mice. The meager literature covering ingestion of refined mineral oil and lubricating oils is presented, if only to call attention to the design of the reported experiments.

1. Acute and Subacute Toxicity

In this subsection, experiments of similar design, using animals of the same species, have been grouped together under the term "oil". This category includes both lubricating oils for automotive, industrial and occupational uses, and medicinal mineral oil (which is a highly refined, non-aromatic product extracted from lubricating oil distillates). The reason for this grouping together is simply that the acute toxicologic effects are generally similar for these two types of oil.

a. oil mist toxicity

Research is presented on exposure of mice and rats to oil mists or aerosols.

(1). mice

S.A.E. 10 automotive lubricating oil (viscosity close to that of SGF No. 2) was nebulized, and six 25-35-gram albino mice were exposed to the oil mist for 2 hours, following which two mice were immediately killed. Two more were sacrificed after 48 hours and the last two were sacrificed after 96 hours. The mass mean diameter of oil droplets was 2.7 μ, and the aerosol concentration was 4330 mg/m^3.

In the mice exposed for 2 hours and killed after 96 hours, the lungs had variable amounts of retained oil after osmic acid staining. Heaviest con-

centrations of oil were seen around the terminal bronchioles and alveolar ducts.

The mice killed immediately after exposure showed vigorous oil phagocytosis, which was complete after 48 hours. A few free oil droplets were occasionally noted in 96-hour lung sections. Except for the presence of a few macrophages, no inflammatory changes were noted in the lungs.

Six albino mice, weighing 25-35 grams, were exposed to liquid petrolatum aerosols for 2 hours. The oil aerosol concentration was 4500 mg/m^3; mean mass droplet diameter was 2.2 μ. Two mice died -- the first one 24 hours following the exposure and the second two days after the exposure. Lung sections were histologically identical to those taken from the 6 mice exposed to S.A.E. 10 automotive lubricating oil for 2 hours (see above) (69).

Seven albino mice, 25-35 grams body weight, were exposed to S.A.E. 10 automotive lubricating oil aerosol, in concentrations of 4330 mg/m^3, mean mass droplet diameter of 2.7 μ, for 92 hours (actual exposure schedule not specified). There were 6 survivors (86%). Lung sections stained with osmic acid disclosed a heavy retention of oil droplets of all sizes in all subdivisions of the respiratory tree (trachea, bronchi, bronchioles and alveoli). Giant droplets ($\geq$ 30 μ in diameter) were seen in all locations, probably resulting from coalescence of many smaller droplets. The majority of droplets were intracellular. Macrophages were numerous and swollen with oil droplets. There were occasional areas of oil pneumonia (69).

Ninety-hour exposures of 13 albino mice weighing 25-35 grams to 4500 mg/m^3 of liquid petrolatum aerosol (actual exposure schedule not specified) permitted the survival of 10 animals (74%). Lung sections stained with osmic acid revealed the same changes as in the mice exposed to S.A.E. 10 automotive lubricant for 92 hours (see above) except that in this experiment, the oil retention was more pronounced. One mouse that died during the experiment had patches of acute inflammation, with polymorphonuclear cells and large numbers of oil-laden macrophages seen in alveoli and bronchioles, while the alveolar elastic tissue remained intact. These changes were characteristic of acute lipoid pneumonia (69).

Albino mice, weighing 20-25 grams, were exposed to oil aerosols, in concentrations of about 200 mg/m^3, for 4 hours. The oil used was either S.A.E. 10-20 automotive lubricating oil or mineral oil, and the results, to be discussed, were identical regardless of which oil had been inhaled. The number of exposed animals was "about 30".

Some mice were sacrificed immediately after exposure, and were found to have developed a hyperplastic tracheobronchial epithelium with some superficial desquamation. Similar hyperplasia was observed in mice killed 18, 24, 48, 72, 96 and 144 hours after the 4-hour exposure. While only a few macrophages were visible in the alveoli of the immediately killed mice, the number of alveolar macrophages steadily increased in animals killed at the later times, reaching a maximum (but still very mild) at 96 hours. The

macrophagic reaction, cells with foamy cytoplasm and fine vacuolization, was also observed occasionally in unexposed mice. There was no localization of macrophages or any indication of oil pneumonia (27).

When mice were exposed to either of the above-mentioned oil aerosols, 200 mg/m^3 for 7 hours a day for 4 consecutive days, no pathologic lesions in the lungs could be demonstrated in animals killed either 24 hours or 96 hours following the last exposure (27).

(2). rats

Twenty male Wistar rats (average weight 200 grams) were exposed to mineral oil aerosols for 6 hours a day for up to 3 weeks. Aerosol concentrations were 30,000 mg/m^3, with droplet diameters of approximately 0.3-0.5 μ. Beginning in the second week of exposure, lung examinations revealed an increase of macrophages and foam cells in the alveolar septae and alveolar lumina in close proximity to mineral oil deposits, which were visible, microscopically, by dark field illumination.

The macrophages and foam cells showed a high enzyme activity of nonspecific esterases and acid phosphatases. There was a clear decrease in adenosine triphosphatase activity.

By the third week of exposure to the mineral oil aerosol, the lungs showed focal granulomas, consisting primarily of histiocytes with only a few foam cells remaining. This condition exemplified classic lipoid pneumonia with oil granuloma formation (101).

b. aspiration toxicity in rats

Five male albino Wistar rats (200-300 grams body weight) aspirated 0.2 ml of S.A.E. 10-20-30 automotive lubricating oil. The mortality after 24 hours was 1 in 5. Other rats, in groups of 5 animals each, aspirated equal quantities of crankcase oil or automatic transmission fluid (more viscous lubricating oils than SGF No. 2), with no deaths resulting within 24 hours of the experiment.

All rats were sacrificed 24 hours following aspiration. Lung weights were nearly normal, indicating little fluid congestion. The lubricants produced a low-grade, localized oil pneumonia in the rat lungs. The lubricating oils had no irritating effect upon direct contact with the alveolar epithelium, except for the slight inflammatory response characterized as oil pneumonia. The author noted that the viscosity of these oils caused some difficulty in getting the animals to aspirate them, unlike benzene, for example, which, being much less viscous, was easily aspirated into the rat lungs (93).

c. ingestion toxicity

The acute toxicity of white (refined) mineral oil ingestion in rats, mice and monkeys is presented.

(1). mice

In groups of mice fed 0.5 ml of white mineral oil per mouse per day mixed with the diet (20 ml/kg body weight) the animals developed rough dry skin, erect hairs, restlessness and weight loss after 3 to 5 days. All animals died after 7 to 10 days on the experimental diet. A group of control animals, fed the same diet with equivalent amounts of mustard oil, was free from all symptoms.

Histopathological examination of organs and tissues revealed diffuse fatty degeneration of liver parenchyma, proliferation of reticulo-endothelial cells of the splenic pulp, marked hypertrophy and hyperkeratosis of the epidermis, and degenerative changes in the ascending renal tubules (102).

(2). rats

Rats were placed on a diet containing 1.0 ml of white mineral oil per rat per day (5 ml/kg body weight). In 3 to 5 days, the animals developed rough dry skin, erect hairs, restlessness and weight loss, and by 7 to 10 days after the start of the experimental diet, all animals had died. A group of control rats, fed the same diet with equivalent amounts of mustard oil, was free from all symptoms.

Organ histopathology revealed diffuse fatty degeneration of hepatic parenchyma, reticulo-endothelial cell proliferation in the splenic pulp, marked epidermal hypertrophy and hyperkeratosis, and degenerative changes in the ascending tubules of the kidney (102).

(3). monkeys

A 2.7 kg male monkey was fed 6 ml per day, 6 days a week of white mineral oil (2.2 ml/kg of body weight). The total amount consumed was 96 ml in 16 feeds. The animal lost 230 g after one week, and in the third week it developed diarrhea and died. Post mortem findings included intense liver congestion, small ulcers and chronic inflammation in the large intestine, and heart, lung, spleen and kidney congestion (103).

A 4.1 kg female monkey was given daily doses of 4.5 ml of white mineral oil in the diet (1.1 ml/kg body weight), for a total of 36 ml in 8 feeds. The monkey developed diarrhea and lost 680 g in one week, and died on the 11th day. Pathological findings were similar to those of the first monkey, including liver, spleen and heart congestion.

The chief action of the white mineral oil, in both cases, seemed to be on the blood vessels, causing increased vascularity and/or congestion of the internal organs studied (103). However, since no controls and only 2 experimental animals were included in the experiment, the results must be evaluated accordingly.

2. Chronic Toxicity

The chronic experiments which have been uncovered in the literature are

of three types: skin painting, aerosol inhalation, and ingestion. These types will be discussed individually and further subdivided by species. It was, in some cases, impossible to define a particular oil used in an experiment in terms of its degree of refinement, but that the oil was of a lubricating oil quality, and that it was not an animal or vegetable oil was certain. The term "oil" has been chosen to represent both lubricating oils (automotive, industrial, etc.) and medicinal mineral oil. The grouping together of experiments employing these various oils was possible due to their similar toxicological properties.

a. oil mist toxicity

Mice, rats, guinea pigs, rabbits, hamsters, dogs and rhesus monkeys have been chronically exposed to lubricating or mineral oils for periods as long as two years. The pertinent literature is presented.

(1). mice

In 1942, Lushbaugh and Cannon (104) exposed 80 white male mice to aerosols of S.A.E. 10 automotive lubricating oil, for 100 consecutive days, in continuous cycles of 30 minutes of aerosol followed by 30 minutes of room air. Exposure chamber oil aerosol concentrations were 132 mg/m^3; oil droplets had an average diameter of 1.2 μ, with a range of 0.7-3 μ. Mice were killed at weekly intervals until the end of the experiment. There were two deaths other than sacrifice over the 100-day period. Twenty mice were still alive 45 days after the exposure ended.

Lungs of mice killed at weekly intervals showed a gradual accumulation of macrophages containing oil, which stained red with Sudan III. After one week, oil macrophages were found under the pleura in peripheral alveoli. After 5 weeks, almost every alveolus contained at least one oil macrophage, and subpleural alveoli contained many of these cells. No free oil was ever seen in the alveoli or bronchi. Two animals that died during exposure were found to have similar numbers of oil macrophages as mice that were sacrificed. The tracheobronchial lymph nodes of mice killed after 3 weeks of exposure showed oil macrophage accumulations, but no tissue reaction due to their presence.

After the 100 days of exposure, 20 mice were killed, and the mineral oil content of the total lung and total liver tissue was determined. The lungs and livers of 20 unexposed mice were also analyzed for mineral oil content for comparison with exposed tissues. The total accumulation of oil in lungs of exposed mice was 33 mg, or an average of 1.65 mg per mouse, which represents about 0.4% of the total wet lung weight of one mouse. In the control lungs, no oil was recovered. In the combined livers of the exposed mice, 3 mg of oil were found, representing 0.01% of the total liver weight of one mouse. In control livers, no oil was recovered.

According to the authors' calculations, an average mouse inhaled about 1.9 mg of oil per day in the above experimental oil exposure conditions. At the end of 100 days, the average mouse lung contained only 1.65 mg of oil indicating that only about a hundredth of the total amount of inhaled oil was retained in the lungs.

No significant reaction to the oil in situ was observed, indicating the possibility that exposure to the oil mist had no significant detrimental effect. The absence of any appreciable number of spontaneous deaths during the 100 days of exposure was further confirmation of the lack of toxicity of the S.A.E. 10 automotive lubricating oil aerosol (104).

In an experiment by Wagner et al. (105), 120 CF No. 1 mice were exposed to aerosols of a non-aromatic lubricating oil with a viscosity similar to SGF No. 2. The aerosol concentrations were 5 and 100 mg/m^3; mass median droplet diameter was approximately 1.3 μ, and exposure time was 6 hours a day, 5 days a week for 12 months. There were 60 unexposed controls.

Body weight increases were the same in control and exposed animals. No hematologic abnormalities were detected in mice exposed to either 5 mg/m^3 or 100 mg/m^3 oil mist for 12 months. There was no major pathologic pulmonary response to either oil mist concentration after 12 months. Small clumps of macrophages were scattered randomly throughout the lungs. The cytoplasm of these cells was occasionally sprinkled with numerous minute clear vacuoles. Lymphatic tissue adjacent to the bronchi contained slightly greater numbers of oil macrophages than that found in control animals.

The spleen, stomach fundus, duodenum, adrenal, liver, kidney and heart showed no histological changes attributable to oil mist exposure (105).

Twort and Twort, 1935 (100) reported on some work they had done in which mice were exposed to mineral oil fumes, produced by heating on an electric plate to induce thermal cracking. There was no definite evidence that the oil fumes caused an increased incidence of lung tumors. There were more frequent catarrhal changes in the lungs of the exposed mice than in controls. There were also indications of a higher average neutrophil count in exposed animals.

(2). rats

Wagner et al., 1964 (105) exposed 160 male Holtzman-Sprague-Dawley rats to aerosol concentrations of 5 and 100 mg/m^3, mean droplet diameter 1.3 μ, of a non-aromatic mineral oil similar in viscosity to SGF No. 2 oil, for up to 26 months (6 hours a day, 5 days a week). There were no changes in weight gain when compared with 85 unexposed control rats. No significant ($p<0.05$) hematologic changes were observed throughout one year of exposure to 5 mg/m^3 or 26 months of exposure to 100 mg/m^3 aerosol concentrations. None of the rats exposed at the 5 mg/m^3 level presented any significant changes in serum or lung alkaline phosphatase activity. The 6-month 100 mg/m^3 exposed rat sera exhibited an 84% increase in basic alkaline phosphatase (BAP) activity over controls ($p>0.02$), and a 58% increase ($p>0.05$) in magnesium activated alkaline phosphatase (MgAP), neither of which was statistically significant. At one year, the sera of rats exposed to 100 mg/m^3 showed very significant changes ($p<0.005$), with 64% and 41% increases, respectively, for BAP and MgAP, indicative of pulmonary tissue damage.

The rat lung tissues showed a progressive reaction to oil inhalation, with increasing numbers and clustering of oil-filled macrophages as the duration of exposure increased. There were varying degrees of interstitial pneumonitis. Hilar lymph nodes were unchanged, save for occasional nodular hyperactivity (not further described) in the 100 mg/m^3 rats. Lung tissue alterations were noteworthy only after exposures to the higher concentration.

The spleen, stomach fundus, duodenum, adrenal, liver, kidney and heart showed no histologic changes which were attributable to oil mist exposure (105).

Spindle oil (lubricant) aerosols, in concentrations of 10-125 mg/m^3, droplet diameters under 5 μ, were administered to male albino rats, 4 hours a day for 5 months. Antibody titers to typhoid and paratyphoid vaccine, and the phagocytic activity of the blood of non-vaccinated animals with respect to non-virulent *Staphylococcus aureus* became significantly lower ($p<0.05$) than in control rats. Spindle oil reduced the immune response even in the lowest concentration inhaled (10 mg/m^3) (106).

The effect of aerosols of lubricating oils without additives on immune reactivity of rats was investigated by Lutov (1973, 107). Ten rats were exposed to axle and machine lubricating oil aerosols in concentrations of approximately 60, 30 or 13 mg/m^3, for 6 months. Neuraminic acid content in the blood (mean for 10 rats) rose from pre-exposure levels around 75 mg% to 107, 98, and 84 mg% for the aerosol concentrations of 60, 30 and 13 mg/m^3 after 3 months, respectively, and to 114, 100 and 88 mg% for the respective aerosol concentrations after 6 months. After a one-month recovery period, neuraminic acid levels fell to 91, 85 and 81 mg% for the same respective exposure concentrations. The two oils did not differ from each other with regard to the neuraminic acid effect. The animals also showed lowered albumin, and increased alpha 1, alpha 2, and beta globulins, lower serum agglutinin titers, and decreased leukocyte phagocytic activity. These changes occurred to a degree which was directly proportional to the oil mist concentrations to which the rats were exposed. The albumin, globulin, and neuraminic acid changes were thought to be consistent with the presence of an inflammatory response and depressed immune reactivity (107).

In a similar experiment by Lutov (1974, 108), white male rats were exposed to aerosols of the same lubricating oils without additives in concentrations of 13, 30 or 60 mg/m^3 for each oil, with 15 animals in each exposure group plus a control (unexposed) group. The experiments were conducted for 5 hr/day for up to 6 months. After 1 month, there was a decrease in weight gain, lower O_2 requirement, reduced respiratory rate, reduced leukocytic phagocytosis, increase in leukocytes, higher levels of neuraminic acid in the blood and a higher neuromuscular excitability threshold. There was considerable pulmonary inflammation, as well as degeneration in the liver, kidneys, adrenals and myocardium. There were no differences in the toxicological effects of the two oils tested.

The acute rise in the blood leukocyte count and shift to the left in the differential noted after one month was followed by a chronic leukopenia, with lower neutrophil and higher lymphocyte counts after six months. Cardiovascular effects such as lower arterial pressure, slower atrioventricular and

intraventricular conductivity, slower heart rate and lower voltage of EKG peaks were attributed to increased parasympathetic tone and adrenal dysfunction. Lower respiratory rates and higher neuromuscular excitability threshold were probably due to the central nervous system depression. Serum protein showed decreased albumin and an increased alpha 1, alpha 2 and beta globulins. At the end of the exposure period there was a marked reduction in neutrophil phagocytic activity, lower agglutinin titers, and higher neuraminic acid levels in the blood.

Following a 1-month recovery period, most changes returned to normal, except that neutrophil phagocytosis and certain agglutinin titers remained substantially lower in animals exposed to 60 and 30 mg/m^3 than in the control animals.

Lung changes after the 6-month exposure included inflammation of alveolar walls, which were thickened by leukocytic infiltrates and connective tissue proliferation, lymphocytic peribronchial infiltrates, and large perivascular and peribronchial leukocytic infiltrates.

Liver, kidneys and adrenals were markedly degenerated. In spleen and lymph nodes, hyperplasia of the reticular stroma and lymphoid tissue were noted, and related to the immunologic changes in the exposed rats (108).

(3). guinea pigs

Ten guinea pigs were exposed to spindle oil (lubricant) aerosols in concentrations of 10-75 mg/m^3, droplet diameter under 5 μ, for 4 hours a day for 5 months. There were significantly lower ($p<0.05$) antibody titers to typhoid and paratyphoid vaccine, and reduced phagocytic activity of the blood of non-vaccinated guinea pigs to non-virulent *Staphylococcus aureus*, than in unexposed controls. This reduction in immune reactivity was evident even at the lowest spindle oil aerosol concentration tested (10 mg/m^3) (106).

(4). hamsters

There were 218 male Golden-Syrian hamsters (and 110 controls) used in an experimental exposure to a non-aromatic mineral oil with a viscosity similar to SGF No. 2, in aerosol concentrations of 5 and 100 mg/m^3, mean droplet diameter approximately 1.3 μ, for 5 days a week, 6 hours a day for as long as 26 months (105).

There were no differences in weight gain between the exposed and control animals. There were no hematologic changes after 1 year of exposure to 5 mg/m^3 or after 26 months of exposure to 100 mg/m^3 of oil aerosol. The lung tissue of only one hamster (exposed for 9 months to 100 mg/m^3) produced increased basic alkaline phosphatase and magnesium activated alkaline phosphatase enzyme activities, which were 216% and 207% ($p<0.01$) greater than activities of control hamsters, respectively, indicating pulmonary tissue damage.

No major lung tissue response was discovered, although the greatest magnitude of response occurred in animals exposed for 15 months to 100 mg/m^3

of oil aerosol. In a few hamsters there were small numbers of finely vacuolated foamy macrophages in alveoli. Some control and experimental animals showed a moderate chronic bronchitis and patches of interstitial pneumonitis.

The spleen, stomach fundus, duodenum, adrenal, liver, kidney and heart showed no histologic changes related to oil mist exposure.

(5). rabbits

Forty-six male Dutch rabbits were exposed to oil aerosols of a non-aromatic mineral oil with a viscosity similar to SGF No. 2 for 6 hours a day, 5 days a week, for up to 26 months. Two oil aerosol concentrations tested were 5 and 100 mg/m^3, with 1.3 μ approximate mean droplet diameters (105).

There were no changes in weight gain when compared with 26 unexposed rabbits. No significant hematologic changes were observed through 1 year of exposure to 5 mg/m^3 or 26 months of exposure to 100 mg/m^3. Quarterly evaluations of hematocrit, hemoglobin and white blood cell counts were within normal limits. No significant differences in minute ventilation or oxygen consumption were determined between trimonthly respiratory function tests on rabbits exposed to either 5 or 100 mg/m^3, or between exposed and control animals (less than 10% differentials in O_2 consumption). Neither control nor exposed rabbits showed any significant differences in serum or lung alkaline phosphatase activity at any time during the experiment.

Pulmonary tissue exhibited no response to the inhaled oil. Tracheae and bronchi were histologically unremarkable. Small foci of septal thickening with chronic inflammatory cells were scattered throughout the lung parenchyma of both control and exposed rabbits. There were a few exposed animals with pulmonary alveoli containing scattered foamy macrophages with small cytoplasmic vacuoles. The hilar lymph nodes were histologically normal.

There were no changes in spleen, stomach fundus, duodenum, adrenal, liver, kidney or heart which were related to the mineral oil aerosol exposure.

(6). dogs

Eighteen male mongrel dogs were exposed to an aerosol of light mineral oil (non-aromatic; viscosity similar to SGF No. 2), with approximate mean droplet diameters of 1.3 μ, in concentrations of 5 mg/m^3 or 100 mg/m^2, for 5 days a week, 6 hours a day, for up to 26 months.

There were no differences in weight gain between control and exposed dogs. Quarterly evaluations of hematocrit, hemoglobin, white blood cell counts and differential leukocyte counts showed no changes in control or exposed animals. No differences were determined in basic alkaline phosphatase (BAP) or magnesium activated alkaline phosphatase (MgAP) enzyme activities between the 5 mg/m^3 exposure sera and control dog sera during 12 months. After one year of exposure to 100 mg/m^3, dog sera BAP activity was 99% greater than controls ($p<0.01$) and MgAP activity was 70% greater ($p<0.01$). At 18 months the re-

spective percentage increase in BAP was 112% ($p<0.05$), but the increase in MgAP activity of 62% was not significant ($p>0.05$). These increases indicated lung tissue damage and repair processes.

Respiratory tissue examinations after 6 months of exposure to 5 and 100 mg/m^3 concentrations revealed differing degrees of reaction to the inhaled oil. The tissue response consisted of infrequent foamy macrophages in parenchymal air spaces, sometimes containing clear oil droplets. Hilar lymph nodes contained occasional similar cell aggregations. Tracheobronchial histopathology was normal. Dogs exposed to 100 mg/m^3 presented more diffuse macrophage accumulations. In addition, there were scattered areas of peribronchial and peribronchiolar oil droplets with adjacent non-nuclear cells, foamy macrophages and epitheloid cells. Within the hilar lymph nodes were scattered coalesced oil droplets. Collections of droplets were most prominent around bronchioles, alveolar ducts and small vessels, and were probably within lymphatic spaces. Animals exposed to 100 mg/m^3 for 26 months developed parenchymal granulomas consisting of lymphocytes and macrophages and containing small and large free oil droplets. The granulomas were located within alveoli or near small bronchi, and in hilar lymph nodes. Occasional diffuse pulmonary tissue congestion, sometimes with mildly thickened alveolar septae was seen, but was also present in some control dogs.

Spleen, stomach fundus, duodenum, adrenal, liver, kidney and heart tissue samples showed no histologic changes attributable to oil aerosol exposure, and were similar to tissues from unexposed dogs (105).

(7). monkeys

S.A.E. No. 10 automotive lubricating oil was used by Lushbaugh et al. (1945, 90) to create an oil mist in an exposure chamber in which 6 young rhesus monkeys were caged for 100 consecutive days. The oil mist was generated for 30 minutes, followed by a 30 minute rest (cycles of 30 minutes on, 30 minutes off) for the duration of the experiment. Oil mist concentrations averaged 132 mg/m^3 of air. Oil droplet diameters from 0.68-2.90 μ were measured, average diameter being about 1.2 μ.

Monkey 1, killed after 30 days of exposure, had oily and somewhat thin fur. The heart and abdominal organs were normal microscopically. The lungs had many small raised subpleural granulomas located about the hilus, with no hyperemia. A subacute and chronic hyperplastic panbronchiolitis was present. Fine oil droplets in alveolar macrophages were thinly scattered throughout the lungs, with occasional small accumulations of lymphocytes and polymorphonuclear leukocytes.

Monkey 2, killed after 50 days of exposure, had complete fur loss on large areas of the abdomen, and thin, oily fur on the head and back. The lungs contained fewer subpleural granulomas than found in Monkey 1, along with hyperplastic bronchiolitis. Oil macrophages had larger oil droplets and were more numerous than in Monkey 1. Many macrophages were present in the pleural lymphatics. Other organs were normal grossly and microscopically.

Monkey 3 died 74 days after the start of exposure, with marked fur loss and emaciation. The lungs revealed granulomas and hyperplastic chronic bronchiolitis, with diffuse bronchopneumonia, edema and hemorrhage. There were many oil macrophages containing large or small oil droplets, mostly in the intra-alveolar location, with a few containing large oil droplets in the peribronchial and peribronchiolar lymphatics. Some free oil was present.

The abdominal organs were grossly atrophic and the stomach was shrunken, but otherwise no abnormalities were found.

Monkey 4 died 90 days after the start of exposure, and the external and gross appearance of the animal's organs were similar to that of Monkey 3. The lungs were slightly hyperemic and contained many very small granulomas. The distribution and amount of oil in the lungs were similar to that in Monkey 3. There were small areas of lobular pneumonia and diffuse pneumonitis, with a slightly increased number of perivascular fibroblasts.

Monkey 5 was killed 164 days after the start of the 100-day oil mist exposure. Most fur had grown back and was no longer oily. All organs were grossly normal. The lungs contained as many oil macrophages as those of Monkey 4, but the distribution was different. The macrophages were concentrated around the atria and perivascular and peribronchiolar lymphatics, with increased numbers of fibroblasts and connective tissue in the latter two areas. Many such areas were seen as fibroblastic nodules containing oil-rich macrophages.

Monkey 6 was killed 365 days after the start of the 100-day oil mist exposure. Externally the animal appeared normal, and all organs were grossly normal except the right lung, which was found to be involved in tuberculous pneumonia and caseonodular tuberculosis. The left lung was not involved in this process. Very few intra-alveolar lipophages were seen, and were concentrated in the perivascular, peribronchial and peribronchiolar lymphatic and connective tissues. Much of the connective tissue had formed condensed fibrotic nodules containing oil and macrophages throughout the lung. Oil was not as prominent as in Monkey 5. The large oil content indicated the slowness of oil removal from the lungs.

Chemical analysis of lung tissue revealed that approximately 200 mg of lubricating oil (about 10% of dry weight) accumulated per lung of the monkeys exposed for 100 consecutive days, of which about half was removed from the lung one year after the exposure was commenced.

Wagner et al. emphasized both the failure of large amounts of oil to accumulate and the absence of severe acute and chronic reactions to the oil that did accumulate. Extrapulmonary effects - loss of fur after long exposures - returned to normal after exposure was stopped (105).

b. ingestion toxicity

Lubricating oils generally have a low order of toxicity after oral administration, according to the Encyclopedia of Safety and Health, published by the World Health Organization (109). The oral LD_{50} value was greater than 10 g/kg of body weight. For mineral oil, no LD_{50} value was found in the literature.

The following three studies involving mice or monkeys, illustrate the systemic toxicity which has been observed.

(1). mice

Skin painting of mice with mineral oil has led to the observance of a liver "condition x", which the authors believed to be due to the ingestion of the oil by animals licking their treated skin (110).

"Condition x" consisted of early round cell periportal infiltration, developing into xanthomata of endothelial cells in conspicuous masses scattered throughout the liver. Degeneration followed, giving rise to a picture of fatty infiltration, with large fat globules of undetermined composition.

"Condition x" also occurred in the livers of mice painted with sulfuric acid-treated spindle oil. (H_2SO_4 removes benzo[a]pyrene and other polycyclics from lubricating oils.) A duration of exposure to the oils of approximately 20 to 90 weeks was sufficient to produce "condition x". No other experimental methodological details were given.

Other organs showing occasional evidence of "condition x" included spleen, ovary and adrenal glands. "Condition x" was not found in unpainted mice within this 20 to 90 week period (110).

(2). monkeys

One monkey, weighing 2.5 kg, was fed 2.25 ml of white mineral oil per day (1.1 ml/kg of body weight) mixed with the diet, the total consumption being 195.35 ml over 3 months. After 3 months, there were no signs of toxicity, and body weight remained the same. The animal was sacrificed, and the only findings were liver congestion and slight kidney congestion.

The chief action of the white oil was on the blood vessels, leading to increased vascularity or congestion in the kidney and liver (103). In the absence of control animals, as well as the use of only one experimental monkey, the results must be evaluated accordingly.

c. cutaneous toxicity

Hyperkeratosis, acanthosis and other skin reactions have occurred in calves and guinea pigs after cutaneous application of lubricating and mineral oils. Skin sensitization studies are also discussed. Experimental skin cancer is presented in the carcinogenicity section of this chapter.

(1). calves

Insecticides and other preparations have been administered to farm animals by mixing them with certain lubricating oils and spraying or applying the mixture onto the animals' skin. Hoekstra et al. (1955, 25) studied the effect of these oils in healthy Holstein-Friesian calves weighing 54.5-136 kg. A highly refined non-aromatic white lubricating oil of a light viscosity (similar to SGF No. 2) was applied to 2 calves at a rate of 0.13 ml/kg (1/3 oz

per 100 lb) of body weight per day for 8 weeks. No grossly detectable skin changes resulted. A higher viscosity, unrefined pale oil (similar in color to SGF No. 2, and therefore closer to SGF No. 2 in composition than the white oil previously mentioned) applied in an identical procedure to another 2 calves, resulted in a very slight degree of hyperkeratosis, which the authors believed to be of questionable significance.

(2). guinea pigs

Male albino guinea pigs (300-500 g) received applications of mineral oils to the left dorsal skin, the right side serving as an untreated control for each animal. Applications were made every other day for 4 days, with doses around 0.6 ml per animal. Subjective skin evaluations of treated areas were made every other day for 20 days following the first treatment.

One oil sample was characterized as "Mid-Continent [oil source], highly refined [non-aromatic] white oil in the light lubricating oil viscosity [viscosity of SGF No. 2] range." The only skin effect was slight erythema and desquamation. Another sample, "Mid-Continent pale oil (not refined) of high viscosity" was mildly active, producing some desquamation and thickening.

The first oil described (white oil), was fractionated, and it was found that the lower boiling fractions, representing 30% of the white oil, boiling range 272-333°C, were strongly active in producing hyperkeratosis in guinea pig skin, whereas the rest of the material boiling from 340-402°C was essentially innocuous.

Further separation of hydrocarbon classes in a light mineral oil showed that n-paraffins with 19-22 carbon atoms were minimally active in guinea pig skin, branched paraffins of C_{22}-C_{25} were innocuous, monocycloparaffins, C_{23} and higher were innocuous, polycycloparaffins C_{22}-C_{23} were innocuous, but mono- and dicyclic aromatic hydrocarbons C_{22}-C_{24} were extremely active in producing hyperkeratosis. This could explain the difference in effect of refined and unrefined lubricating oils on guinea pig skin (85).

Hyperkeratosis in guinea pig skin was also found to occur after applications of 1-methylnaphthalene, dodecylbenzene and decalin. In a procedure similar to that used above, the shaved ventral skin on one side of each animal was painted for 10 days with the particular substance, the other side serving as an untreated control. Microscopic examination of the treated skin revealed inflammation and a high degree of acanthosis after 1-methylnaphthalene, and severe thickening after either dodecylbenzene or decalin were applied (dose not specified) (111).

Liquid paraffin was reported to have no acanthogenic activity, while another drug-grade mineral oil produced moderate skin thickening, and colored (less well refined) mineral oil was highly acanthogenic.

After testing various fractions of mineral oil, the author found that acanthogenic activity increased as molecular weight decreased, and as viscosity decreased. C_{20} and larger n-paraffins were harmless. C_{20} and larger monocycloparaffins were nearly inactive. High molecular weight aromatic

compounds, such as those found in petrolatum jelly, were also harmless when applied to guinea pig skin (there was no mention of the quantity of substance applied) (111).

The effect of liquid petrolatum (U.S.P. grade) on cutaneous reactivity of albino guinea pigs previously sensitized to 2,4-dinitrochlorobenzene (DNCB) was tested by Rebello (84). Guinea pigs were sensitized with one intracutaneous injection of 0.1 ml of a 0.05% solution of DNCB in 50% alcohol-saline. Two weeks later, doses of 0.1 ml of DNCB were applied to this area and also to an untreated skin area of the same animal, and the degree of skin erythema and swelling were recorded.

Three groups of 6 sensitized guinea pigs each were exposed twice a day to 0.5 ml of liquid petrolatum for two weeks. The animals exposed daily developed severe irritation; the others were treated every other day or every third day. After 2 weeks and 24 hours following the last mineral oil exposure, the animals were challenged with DNCB.

Erythema followed by scaling and thickening was noted after repeated liquid petrolatum applications alone, the intensity of the reaction being proportional to the frequency of application. Histologically, there was acanthosis, hypergranulosis and hyperkeratosis of epidermis and hair follicles, with mild inflammation of the corium. Skin reactions following the challenge with DNCB were more numerous and intense on the sensitized skin treated with liquid petrolatum than on sensitized skin which had not been exposed to oil. The treated side showed spongiosis and some cases of vesiculation accompanied by prominent lymphocytic infiltration and capillary dilatation in the upper corium. Mild inflammation and capillary dilatation were the only findings on the untreated skin after the DNCB challenge.

The increased reactivity of guinea pig skin to the sensitizer DNCB, caused by pretreatment with U.S.P. mineral oil, was explained by the acanthogenicity of the oil. Acanthotic skin was thought to provide a larger quantity of protein for conjugation and conversion of a simple chemical into an antigen. Another explanation offered that mineral oil caused an enhanced permeability of the skin to DNCB, or that the presence of macrophages and lymphocytes in the mineral oil-treated area increased the degree of sensitization of guinea pig skin (84).

3. Carcinogenicity

The inhalation of lubricating oil mist, oil smoke, and white mineral oil mist in various species is discussed in terms of lung cancer. Skin painting and induction rates of skin cancers in mice are also presented. It may be helpful to the reader to refer back to the Physical and Chemical Properties section dealing with SGF No. 2 Models in order to better understand the chemical composition of carcinogenic oils. There will, however, be some repetition between this material and the above-mentioned chapter.

a. lung cancer

Inhalation studies in mice and guinea pigs are presented.

(1). mice

In 1935, Twort and Twort reported their experimental results of exposing mice to mineral oil fumes, which were created by heating the oil on an electric plate to induce thermal cracking. They found no definite evidence of an increased incidence of lung tumors in exposed mice (100). The experimental setup was not described.

Lubricating oils recovered from the sump of motor vehicles were more carcinogenic than unused (new) automotive lubricating oils. Liquid paraffin and Texas engine oil had very minimal carcinogenicity before cracking, but the potency increased about thirty-fold after cracking on an electrically heated plate. It is unfortunate that in the experiments mentioned above, the methods were not reported in greater detail than what appears here (100).

Another experiment which was performed by Schepers (1971, 112) involved exposing 20 mice to "oil smoke" (not further described) 16 times a month (no other information given). In these 20 mice, 12 lesions developed, whereas unexposed control mice remained tumor-free. There were 3 pulmonary neoplasms, 5 alveolar epithelializations and 4 other pulmonary lesions.

The genetically based, spontaneous pulmonary tumor-susceptible CAF_1/Jax mouse was used as a possible indicator of any potential tumorigenic accelerating or inhibiting capability of an aerosol of a non-aromatic mineral oil with a viscosity similar to SGF No. 2 (105). There were 250 non-exposed controls, as well as 250 CAF_1/Jax mice exposed to oil aerosol concentrations of 100 mg/m^3, for 6 hours a day, 5 days a week for 16 months. Serial, random samples of lungs of exposed and control mice were taken after 7, 9, 10, 11, 12 and 13 months of exposure, in order to provide a sensitive indicator of tumor inhibition or acceleration in susceptible mice.

Gross and histologic examinations of lung tissue revealed mild tumor acceleration - 20% and 15% after 10 and 11 months of oil mist exposure, respectively, compared with unexposed CAF_1/Jax mice. Serial sacrifices after 12 and 13 months revealed that the number of tumors in oil mist exposed animals was less than expected, if the oil mist is considered to be an accelerator (4/20 exposed vs 6/20 controls at 12 months, and 9/40 exposed vs 14/40 controls at 13 months). In the controls, however, there was a continuing progression of mice with tumors over the entire 13-month period. These findings were thought to be indicative of an alteration by the oil of the mechanism responsible for the tumorigenic activity. The spontaneity of lung adenoma formation could have been activated by the presence of the relatively inert oil droplets trapped in the pulmonary alveoli, which could act as a foreign body insult. According to Wagner et al. (105), evidence of an altered rate of tumor formation at the 100 mg/m^3 oil aerosol concentration was "equivocal".

(2). guinea pigs

After inhalation of mineral oil aerosols by 40 guinea pigs for 24 exposures per month, 1 pulmonary neoplasm, 8 cases of alveolar epithelialization and 17 other pulmonary lesions were found. No tumors developed in control guinea pigs. Unfortunately, the duration of the experiment, concentration of the aerosol and nature of the 17 other pulmonary lesions were not specified by the authors (112).

In 40 guinea pigs given 24 exposures per month to "oil smoke" (no description of oil smoke, duration of exposure nor concentration of smoke was provided) pulmonary effects included one neoplasm, 4 cases of alveolar epithelialization and 9 other pulmonary lesions. No tumors were observed to develop in unexposed controls (112).

b. skin cancer in mice

In 1957, the influence of various hydrocarbons on the rate of induction of tumors of the skin of C3H mice by methylcholanthrene or benzo(a)pyrene was investigated by Horton et al. (113).

A viscous white mineral oil, chiefly composed of cycloparaffins with 20 or more carbon atoms, and containing (added) benzo(a)pyrene, 0.20% by weight, was applied to the dorsal skin of 18 mice, in doses of 50 mg, 3 times a week until papillomas appeared. The average duration of tumor-free life was 28 ± 3 weeks, as compared to an expected duration of 29 weeks if no tumor acceleration occurred. The mineral oil was therefore classified as a non-accelerator.

Other substances (some of which are present in lubricating oils) were tested in a similar manner. *t*-Dodecylbenzene with 0.17% methylcholanthrene or benzo(a)pyrene, applied three times a week in 100 mg doses to 16 and 18 mice, respectively, gave 9 ± 1 weeks and 11 ± 2 weeks of tumor-free life (expected values were 30 and 33 weeks). It was a potent accelerator. *n*-Dodecane, 0.20% benzo(a)pyrene, 50 mg three times a week reduced tumor-free life from 33 weeks (expected) to 15 ± 1 weeks, and was also a potent accelerator. 7-Phenyltridecane (an alkylbenzene) in 40 mg doses, di-sec-amylnaphthalenes (boiling range 330-370°C) in 50 mg applications, and 1-cyclohexyldecane (a cycloparaffin) in 20 mg doses, were all potent accelerators of papillomas in C3H mouse skin.

The dodecylbenzene applications (100 mg, three times a week) produced primary skin irritation, with sloughing and hair loss after 2 weeks, hyperkeratosis after 4-5 weeks and acanthosis, but the skin changes had no correlation with tumor accelerating activity.

Dodecylbenzene and alkylbenzene mixtures produced no tumors when applied alone, 3 times a week, 100 mg per dose, to 20 mice, over a period of 68 weeks. Six animals survived (113).

By 1958, Cook et al. (23) had seen tumors in the skin of mice painted with lubricating oils, and also knew of the skin and scrotal cancers in mule spinners in the cotton industry and machinists in the metal mnaufacturing industry. He stated that up to that point, no pure carcinogen had ever been isolated from uncracked crude oil distillates; he then set out to separate and characterize the carcinogenic fractions, in hopes of identifying the substances responsible for their activity.

His experiments involved fractionating crude oils from three sources: Kuwait, Lagunillas and Oklahoma. By reducing the pressure in the fractionating column, he was able to avoid thermal decomposition, i.e., cracking and the possible formation of new, carcinogenic substances. One fraction

with especially high skin cancer-producing activity in rabbits, and slight activity in mouse skin, boiled between 350-400°C. It was found that the aromatic hydrocarbons present in this fraction were responsible for the carcinogenicity, because when these were extracted with aqueous acetone or furfural (which selectively remove polycyclic aromatic components from lubricating oils), the carcinogenic activity passed almost entirely into the extracts, which amounted to about 20% of the 350-400°C fraction. Reaction of the aromatic extract with maleic anhydride removed a portion containing anthracene derivatives. The anthracene portion was a relatively inactive carcinogen. The remaining part of the extract, treated with picric acid in ethanol, yielded two fractions which were actively carcinogenic, but most activity was in the mother liquor. The two fractions were chromatographed on alumina, and the carcinogens could be largely concentrated by elution with petroleum ether and with benzene. They included: 1,8-dimethylphenanthrene, 1,2,8-trimethylphenanthrene, tetramethylphenanthrene, tetramethylfluorene, 1-methylpyrene, 1,2-benzofluorene, 8-methyl-1,2-benzofluorene, 1,8-dimethyldibenzothiophene, 1,2,6,7-tetramethyldibenzothiophene, 3-ethyl-6,8-dimethylnaphtho(1,2-b)-thiophene and pentamethylcarbazole. The maleic anhydride extracts (anthracene portion) contained: 2,6- and 2,7-dimethylanthracene, 2,3,6-trimethylanthracene, 1,3,5,7-, 1,3,6,7- and 2,3,6,7-tetramethylanthracene, and four unidentified tri- or tetramethylanthracenes.

The substances in the picric acid-ethanol fractions were polycyclic aromatic hydrocarbons of a degree of complexity approaching that of then known polycyclic aromatic carcinogens, namely benzo(a)pyrene, and thus it was conceivable that they might be weakly carcinogenic and contribute to the total activity of lubricating oils.

The Kuwait oil was also very high in sulfur content, and spectrographic evidence indicated that many carcinogenic fractions contained considerable quantities of dibenzothiophene derivatives as well as other condensed polycyclic thiophene compounds. A number of condensed tetracyclic thiophene derivatives were already known to have powerful carcinogenic activity (23, 62).

Benzo(a)pyrene had been extracted from industrial lubricating oils with sulfuric acid, in order to protect employees from skin cancer. The fact was that these other polycyclic aromatic hydrocarbons separated by Cook et al. could not be extracted with sulfuric acid, but only with furfural, phenol or cresol (62, 66).

Ellis (62) reviewed the work of Bingham (1965), who investigated the carcinogenicity of both solvent refined lubricating oils and sulfuric acid treated and filtered lubricating oils. Test groups of mice were treated with 50 mg of undiluted oil twice weekly for 80 weeks. The basic test group was 15 mice, but if no tumors developed by the end of 26 weeks, another 15 mice were added. One oil sample, with a viscosity similar to SGF No. 2, which was acid refined and had no additives, produced 9 malignant tumors in 15 mice. No benign tumors were found. Using the same experimental set-up, a solvent refined oil was reported to be non-carcinogenic to mouse skin.

In general, irrespective of crude oil source, solvent extraction was deemed superior to sulfuric acid in removing certain carcinogenic polycyclic aromatic hydrocarbons from lubricating oils (62).

In 1967, male Chester-Beatty mice were used to test the carcinogenicity of a batching oil used in the manufacture of jute. This oil, which was not solvent refined, was found to contain detectable levels of benzo(a)pyrene, although the actual concentration was less than 1 µg per gram of oil, i.e., less than 1 ppm by weight. No other polycyclic aromatic hydrocarbons were found after paper and absorption column chromatography followed by ultraviolet spectroscopy (19).

In one experiment, a sub-carcinogenic dose (150 µg in 0.2 ml acetone) of 7,12-dimethylbenz(a)anthracene (DMBA) was applied to the dorsal skin of 24 animals, followed by applications of the batching oil, undiluted, for 4 weeks. This produced inflammation and skin ulcers. After 18 days of healing, mineral oil applications were resumed for 6 further twice-weekly applications. The animals thus received 14 applications of 0.25 ml of batching oil during the course of 9 1/2 weeks. More than 90% (22) of the animals developed first skin tumors in an average of 11 weeks. Malignant tumors occurred in 11 animals, of which there were 9 squamous cell carcinomas, 1 basal cell carcinoma and 1 sarcoma. Benign lesions predominated, namely, 22 squamous papillomas.

In 24 animals treated with batching oil but not with DMBA, in the same application schedule as the group described above, 6 animals developed malignant skin tumors in 84 weeks, with an average induction time of the first tumor of 20 weeks. Some of the skin tumors were of unusual histological types; they included 1 sarcoma, 2 carcinosarcomas, 3 squamous cell carcinomas, and 2 benign squamous papillomas.

DMBA alone, in the 150 µg dose, had negligible carcinogenicity. Control mice receiving neither DMBA nor oil developed no skin tumors in 84 weeks.

Tumors occurring at sites other than the skin included 3 pulmonary adenomas, 2 generalized lymphocytic neoplasms and 3 hepatomas in mice treated with DMBA only. In mice treated with batching oil alone, there were 2 pulmonary adenomas, 3 generalized lymphomas and 2 hepatomas. Untreated mice developed 1 each of pulmonary adenoma and hepatoma, and 5 generalized lymphomas. No distant tumors were found in mice receiving the DMBA and batching oil. These lesions were stated to be common in Chester-Beatty stock mice (19).

Horton, in 1973 (114), tested the carcinogenicity of a highly cycloparaffinic extract of lubricating oil, with a viscosity similar to SGF No. 2. The material was rich in 2- and 3-ring cycloparaffins.

The co-carcinogenic activity was determined by adding 0.14% by weight of benzo(a)pyrene to the oil and applying this repeatedly to the intercapular area of male C3H mice (15-20 animals per group). As a control, a solution of 0.14% benzo(a)pyrene in a non-carcinogenic vehicle (decahydro-

naphthalene) was applied to another group of mice. The average tumor-free life of the experimental and control animals (until one papilloma appeared) was compared. The controls remained tumor-free for about 37 weeks, while the cycloparaffinic oil treated group remained tumor-free for 33 weeks.

To determine inhibiting activity, three 50 µl doses of 0.4% dimethylbenzanthracene (DMBA) in benzene were applied to the skin in one week. After a 3-week interval, the oil was applied twice a week to the same skin area, until tumors appeared. Control animals receiving only DMBA had a 35% tumor production rate, while oil treatment retarded the appearance of tumors initiated by DMBA. The rate was as low as 40% as many tumors as in the controls. This oil was, then, a definite inhibitor to latent cancer initiated by DMBA (114).

Another oil which was tested was described as a lubricating oil extract rich in n-alkanes and monocycloalkanes, with a viscosity similar to SGF No. 2. Using the same methodology as above, this oil was found to be a stronger promotor (co-carcinogen) than the di- and tricycloparaffin-rich oil. In this case, tumor-free life of male C3H mice was 29 weeks, as compared with 37 weeks in the controls.

Gas chromatography of the above oils revealed that n-alkanes containing 17-28 carbon atoms were mild tumor promoters, as compared with C_{15}-C_{16} n-alkanes (not significant in lubricating oils) which possessed a much higher tumor promoting activity. The cycloparaffinic oil was less promoting than the oil rich in n-alkanes. Oils containing mixtures of normal and cyclic alkanes had a modest promoting activity, which was interpreted as a compromise between the effects of active promoters and inhibitors (114).

In 1960, Hueper also had found that highly refined, non-aromatic paraffin oil was capable of producing tumors in mice. Paraffin oil was painted on the skin of the nape of the neck of 50 C57 black mice, 25 of each sex, twice weekly for 24 months, following which the survivors were killed. The oil was found to be mildly carcinogenic; one squamous cell carcinoma, one papilloma, and two leukemias or lymphomas resulted. No other data was provided (115).

V. PHARMACOKINETICS OF FOG OILS IN HUMANS AND ANIMALS

Due to differences in physical and chemical properties between the two fog oils, SGF No. 1 and SGF No. 2, the absorption, distribution, biotransformation and excretion of both fog oils will be treated separately in this chapter.

A. SGF No. 1 Models

Although the absorption, distribution, storage, biotransformation, and excretion of the middle distilla fuels have not been reported in the literature to date, it is likely that the pharmacokinetics of the different hydrocarbon types present in these fuels, e.g., aromatics, paraffins and olefins, would proceed through different mechanisms. Further studies are needed to evaluate this possibility. Reported data include the skin absorption rate of diesel fuel, absorption, metabolism and distribution of normal paraffins from the digestive tract, distribution and metabolism of selected alkyl aromatic compounds, and urinary biotransformation products of aromatic hydrocarbons.

1. Absorption

The general lipid solubility of these fuels allows their absorption through the respiratory epithelium, mucous membranes, gastrointestinal tract and epidermis. In one study by Starek et al. (92), the absorption of diesel fuel through the intact tail skin of Wistar rats was measured and found to be 2.57 ± 0.52 mg/cm^2/hr (the methodology was not detailed). The authors felt that since no rats died, the rate of absorption had been too slow, presumably, to allow accumulation of the fuel in the bodies of the rats.

The normal aliphatic portion of diesel fuel can be represented by octadecane and hexadecane for purposes of studying absorption. It was originally believed that these paraffins were completely unabsorbed and metabolically inert. El Mahdi and Channon (116) found that rats fed n-hexadecane daily for 3 weeks (doses from 0.035 - 0.12 ml) were able to absorb about 7% of the total dose. Because there was no increase in unsaponifiable material in the livers of these rats, they concluded that the substance was either metabolized or stored in an organ other than the liver. Hexadecane was isolated from tissue lipids after prolonged feeding of the substance to rats (117). Stetten, Jr. (117) found that growing rats absorbed about 80 mg/day of deuterated hexadecane, of which 15% of the isotope was recovered in fatty acids. This was evidence that oxidation took place. The isotope content of the liver was higher than that of the feces, indicating the site of oxidation was not exclusively the gastrointestinal tract. There was no accumulation of unoxidized hydrocarbon in the liver.

The oxidation of normal aliphatics to fatty acids, occurring in the intestinal wall of rats fed deuterated octadecane, hexadecane, tetradecane, dodecane and decane, was studied by Bernhard et al. (118). The reaction proceeds in 2 steps: an intestinal dehydrase removes hydrogen from the 1,2-position; oxidation follows.

The products of this reaction were recovered in the mesenteric lymph. McCarthy (119) found that oxidation occurred in perfused goat rumen prior to absorption into the blood. Hexadecane and octadecane underwent ω-oxidation to fatty acids of the same carbon number. A portion of these hydrocarbons was also absorbed unaltered from the gut and found in liver lipids after 6 hours, as determined from experimental feeding of radioactive octadecane and hexadecane to rats.

Oxidation of radioactive hexadecane occurs in subcellular fractions of guinea pig intestinal mucosa (120). The highest activity was found in the microsomal fraction, although the high-speed supernatant was also active. Microbial enzymes from the flora of the small intestine did not contribute to oxidation. Maximal conversion of hexadecane to hexadecanol and palmitic acid required NAD[1], NADP[2] and glucose-6-phosphate, and the reaction was inhibited by carbon monoxide, indicating involvement of cytochrome P_{450} in oxidation.

The major site of absorption of normal alkanes was found to be the small intestine in rats. There were no differences in uptake among duodenum, jejunum and ileum. Duodenal sections of intestine released radioactive hexadecane and its metabolic products more rapidly than sections of ileum. The primary route of absorption was into the lymph, as determined by cannulation of the intestinal lymph duct. Paraffins with more than 29 carbon atoms were not significantly absorbed, and there were no significant differences between retention of branched, cyclic and unsaturated hydrocarbons and saturated aliphatics with the same carbon number. (Retention was calculated as 100% minus the percentage excreted in feces). In rats injected intraduodenally with radioactive hexadecane in an emulsion of synthetic rat bile, the lymph and blood levels of ^{14}C increased almost linearly over 7 hours. Portal blood was slightly more radioactive than heart blood, suggesting the possibility of direct absorption of the hydrocarbon or metabolites into the portal circulation. The authors postulated that absorption of aliphatic hydrocarbons involves emulsification in the gastrointestinal tract, some absorption of intact molecules into the lymph, and some oxidation to fatty acids of the same carbon number at the time of absorption (121).

The absorption of radioactive hexadecane after topical application to the skin of male albino guinea pigs for 48 hours was about 20% of the total applied dose. Mineral oil, docosane and heptane reduced the penetration of the labelled alkane, while repeated applications of hexadecane increased its uptake (122). It is proposed that heavy mineral oil and alkanes over 20 carbons long reduce the dermatotoxic effect of hexadecane by interfering with its penetration to the site of action, which appears to be deep in the epidermis. The use of protective pastes on the skin to reduce dermatitis after exposure to industrial solvents and fuels is based on this observation. The mechanism of the protective effect may be either one of simple dilution or a more specific interference of penetration.

[1]NAD - nicotinamide-adenine dinucleotide
[2]NADP - nicotinamide-adenine dinucleotide phosphate

Aromatic hydrocarbons are absorbed slowly through the skin. Gerarde (8) feels that systemic intoxication with these compounds following topical exposure is improbable for this reason. Absorption of alkylbenzenes, for example, into the bloodstream may cause local irritation of the endothelium and permeability changes in capillaries, leading to edema, petechiae or gross hemorrhage. Alkylbenzenes are absorbed in decreasing levels from the gastrointestinal tract with increased chain length and branching.

In one report of a 2-year-old boy who drank heating oil (composition unspecified) and was given mineral oil therapeutically, it was postulated that the mechanism of absorption involved formation of an emulsion of the oils in the small intestine. Microdroplets of the hydrocarbons then were able to pass into the lymph, and into the bloodstream. An alternate theory is that the oils may have been resorbed by direct passage through the intestinal wall without degradation, in a manner similar to persorption of starch granules. The mechanism remains unknown (123).

2. Distribution

Once in the bloodstream, aliphatic hydrocarbons in the form of free fatty acids are cleared by the liver. McCarthy (119) found that in goats, radioactive octadecane was rapidly cleared from the bloodstream after i.v. administration and there was increased radioactivity in liver phospholipid and fatty acid fractions, indicating that the liver took up the octadecane before conversion to fatty acids.

Bernhard (124) fed rats deuterated octadecane and found the isotope in oleic, palmitic and stearic acids. In another experiment, rats fed labelled octadecane and hexadecane developed deposits of these paraffins in the liver and fatty tissues.

The distribution of octadecane was studied by Popovic (125). After i.v. administration of a radioactive emulsion of n-octadecane to rats, the radioactivity was concentrated in the liver (33%), fat (18%) and spleen (8.3%), while after p.o. administration, the most radioactivity was in the liver (1.28%), fat (0.66%) and intestine (2.41%). This indicates that only a small portion of octadecane emulsion was absorbed from the gastrointestinal tract. Expired $^{14}CO_2$, determined every 30 minutes after administration, was also much lower when the emulsion was given orally than intravenously. The octadecane was incorporated into fatty acids in the liver, especially lecithin.

Goat and rat liver homogenates metabolized hexadecane more readily than carbon chains either longer or shorter than C_{16}, according to McCarthy (119). The microsomal fraction of mouse liver hydroxylates long-chain aliphatic hydrocarbons. Radioactive hexadecane was oxidized in the presence of NADPH[1] and molecular oxygen to palmitate and a smaller quantity of hexadecanol. Mouse lung microsomes showed weak hydroxylation activity, and the kidney microsomal fraction was inactive (126). P_{450} cytochrome involvement was shown by inhibition of the reaction with carbon monoxide.

[1] NADPH - reduced form of NADP

After topical application of radioactive hexadecane in guinea pigs, the dermis contained about 0.1% of the applied dose, and the liver and kidneys a total of about 0.1%. Measurable amounts of ^{14}C were not found in the blood (122).

Alkylbenzenes and related aromatic hydrocarbons are found in the bloodstream adsorbed on lipoproteins or dissolved in chylomicrons, after gastrointestinal absorption, but the majority is bound to red blood cells, due to high lipid solubility of the hydrocarbons. They accumulate in body tissues in proportion to their fat content (8). They may be dissolved in neutral body fat, may enter the nervous system and cerebrospinal fluid and may cross the placenta into fetal blood, as do other lipid soluble substances.

3. Excretion

Excretion of heating oil is briefly discussed in a report of a 2-year-old boy who drank the substance. The oil could be detected spectroscopically in the urine of the child (123). Details were not provided.

In albino rabbits given, orally, various organic compounds at half the single lethal dose, urinary inorganic sulfates and glucuronic acid were determined by quantitative spectrophotometry with a modified Tollens test (127). Kerosene and naphthalene caused a marked increase in glucuronic acid excretion and a slight or moderate increase in urinary inorganic sulfates, usually on the second day after dosing. This may be a valuable method for assessing the extent of absorption of organic compounds in industrially exposed persons.

In comparison with kerosene, diesel fuel is excreted slowly by rats fed large doses, and accumulation of the substance occurred (92).

Excretion of aromatic hydrocarbons, such as alkylbenzenes, occurs either as unchanged hydrocarbons, or as water soluble urinary biotransformation products, conjugated with glucuronic acid, sulfuric acid or glycine. Unmetabolized aromatics may also be exhaled from the lungs (8). Figure 1 shows the curve of aromatic hydrocarbons in blood following a 1.25 ml intragastric dose of kerosene. After an initial rise, the blood concentration fell over the next 12 hours, and by 32 hours, less than 5 ppm could be detected.

Urinary biotransformation products of aromatic hydrocarbons have been studied and the metabolic pathways described. Hepatic monooxygenases convert naphthalene to naphthalene-1,2-oxide, which then either spontaneously isomerizes to 1-naphthol, is enzymatically hydrated to a trans-dihydrodiol, or conjugates both spontaneously and by enzymatic catalysis with glutathione. The conversion of polycyclic hydrocarbons to oxides of phenanthrene and benzanthracene also occurs. Glutathione conjugates are metabolized to premercapturic acids, by loss of glycine and glutamic acid residues, followed by N-acetylation of the substituted cysteine. The premercapturic acids are dehydrated to mercapturic acids (128).

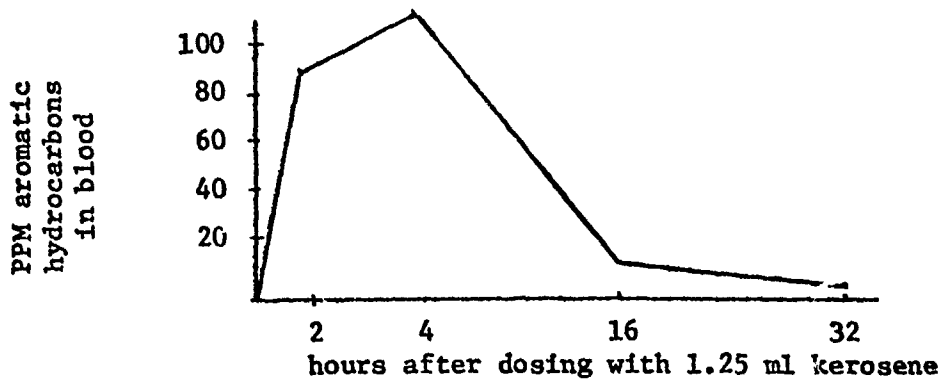


Fig. 1. Absorption-elimination curve for aromatic hydrocarbons in kerosene in rats dosed by gastric intubation (1.25 ml per animal).

Ref: Gerarde (8).

B. SGF No. 2 Models

The absorption, distribution, and metabolic pathways to excretion or storage of lubricating and medicinal mineral oils are discussed, as applicable to humans and other mammals.

1. Absorption

Aerosols of lubricating oils, containing droplets under 5 μ in diameter, are of alveolus-penetrating size. The depth of penetration of particles or droplets into the lung was found to increase with decreasing diameter of the droplets. The percentage of retention increased with increasing size (69). The fact that oil pneumonia (or at least oil droplets inside macrophages in lung tissue and surrounding bronchioles) has been documented in animals inhaling oil aerosols, is evidence of absorption of oil droplets from the pulmonary epithelium (69, 101).

Absorption of lubricating oils from intact skin occurs, at least through the dermis, giving rise to skin responses such as hyperkeratosis, acanthosis and malignancy, as amply illustrated in the Animal and Human Toxicity sections. Hodgson (59) termed the skin a protective barrier, which was either penetrated or broken down by chronic oil exposure.

Absorption of lubricating oils through the gastrointestinal tract has been demonstrated in humans and animals. Medicinal mineral oil was found (histological and chemical studies) in lymph nodes of the portal hepatis in 49 of 61 consecutive autopsies of humans over the age of 20 years (28). In 60 livers and 34 spleens obtained from 63 autopsies, oil droplets were identified as mineral oil. Chemical analyses revealed mineral oil concentrations of 0.11-4.1 mg per gram of liver and 0.14-4.5 mg per gram of spleen. The liver and splenic oil content were thought to be due to drainage of abdominal lymph nodes via the hepatic lymphatic channels (87). Ingestion of mineral oil, either intentionally or by eating processed foods was thought be be responsible for the findings of oil in these locations.

In a series of 400 autopsies, there were 23 cases in which histological evidence of mineral oil in mesenteric lymph nodes was found. In 7 of these cases, oil was found also in the liver and spleen. In 12 of the 23 cases, intestinal tissues could be examined, and one case of oil macrophages in the intestinal wall were described. The correlation between clinical history and oil in mesenteric lymph nodes in the 23 cases was: liquid petrolatum use in 5, laxative use in 7, denial of laxative use in 4, and clinical history unknown in 7 (129).

In humans, about 2% of the normal laxative dose of mineral oil can be absorbed (28).

Ebert et al. (130) studied the absorption of U.S.P. mineral oil after its oral administration to Sprague-Dawley and Holtzman rats. The oil, which was randomly tritiated, was administered in a dose of 0.66 mg/kg of body weight, a dose representative of the recommended human (laxative) dose.

More than 80% of the total dose was excreted without being absorbed. Five hours after administration, 13.8 µg/g of total body weight, or 1.6% of the total dose, was absorbed. This was the highest concentration of mineral oil that was absorbed at any time in the rats. There was no evidence of facilitation of absorption in rats fed 0.66 mg/kg of body weight of mineral oil daily for 31 days.

From these general sites of absorption, i.e., lungs, skin and intestine, the oil is usually found not to have travelled very far, but instead to remain, in small intracellular droplets of macrophages, or in larger, coalesced globules or paraffinomas, close to the site of entry, as amply documented by the histopathological descriptions in animals and humans.

2. Distribution

Gross and histologic findings in animals and humans, as previously discussed, indicate that much of the inhaled lubricating oil which is absorbed is captured in phagocytes and remains dispersed within the lungs or lymph nodes and lymph vessels of the lungs (or in the mesenteric lymph nodes if ingested). The formation of granulomas containing the oil droplets prevents the oil from further spreading. This is supported by the work of Stryker (129), who fed 13 adult white rabbits 20-30 ml of oil per rabbit per day mixed with the diet. After 7 months of feeding the rabbits, mineral oil nodules were present in the gastrointestinal mucosa, mesenteric lymph nodes and liver. The longer the rabbits were given the oily diet, the more granulomas appeared in these locations. Rats fed a diet containing about 5% mineral oil (exact dose not reported) also developed oil granulomas in the mesenteric lymph nodes and the liver, but not in the intestinal mucosa, after 7 months. Guinea pigs refused to consume the oil diet, and were dosed once a day with 1-20 ml of mineral oil per animal. Even after 15 months of dosing, there was very little histologic evidence of accumulation of oil in the liver or mesenteric lymph nodes.

In Ebert's rats dosed with 0.66 ml/kg of tritiated mineral oil, the distribution of the oil after 5 hours was highest in the liver (110 µg/g of tissue), with from 8 to 50 µg/g of fat, kidney, brain, and spleen, or a total in these organs of less than 0.2% of the oral dose (130). Intraperitoneal injection of 0.66 mg/kg of body weight revealed approximately the same distribution in liver, kidney, fat and brain as did oral administration of this dose, after 24 hours, i.e., the liver and fatty tissue contained the highest concentrations of oil, and brain the lowest.

Six young male rabbits (2-3 kg) were intravenously injected with 1 ml/kg of body weight of a paraffin oil emulsion (containing 15% oil labelled with C^{14}-decane). Radiochemical and histological examinations revealed that after injection, the emulsion was rapidly cleared from the bloodstream, and was no longer detectable in blood after 1 hour. The substance was filtered by the liver, spleen, adrenals, bone marrow and lungs. The content of these organs, after 1 hour was: liver > adrenal > bone marrow > spleen > lungs. After 12 hours, a different distribution was noted: adrenal > spleen > liver > bone marrow > lungs. After 1 month, the distribution was

still similar, although much less was present, as indicated by counts per minute per gram of the particular ^{14}C containing tissue. The authors justified their use of decane as a tracer, stating that the total paraffins of mineral oil were similar in behavior and distribution in the organism to decane. Histological methods established that the reticuloendothelial cells of these organs had filtered out the oil emulsion. The Kupffer cells of the liver picked up the oil, which was later found in hepatocytes as small granulomas. In the spleen, red pulp reticulocytes contained the oil; the reticulocytes of bone marrow and both adrenal cortex and medulla contained oil droplets (131).

In cases of lipoid pneumonia due to mineral oil aspiration, not only the lungs, but also hilar and portal lymph nodes, liver and spleen have been found to contain mineral oil deposits and/or paraffinomas (67, 86). Oil in the lungs may be carried by the lymphatics to the hilar lymph nodes and from there be transported into the thoracic duct, entering the systemic circulation and becoming deposited in the liver, spleen or other organs of the body (68).

Medicinal mineral oil has also been found, however, in autopsied tissues and organs of persons with no evidence of lipoid pneumonia, and dubious histories concerning mineral oil laxative ingestion. In one report by Boitnott and Margolis (28), lymph nodes taken from the porta hepatis of 49 of 61 consecutive autopsies of humans over the age of 20 were examined histologically and analyzed chemically for the presence of mineral oil.

In 38 cases (78%) large oil droplets (100 μ diameter) were present in the lymph nodes. Small intra- and extracellular oil droplets and multinucleated giant cells were seen adjacent to the larger droplets. Saturated hydrocarbons were detected by thin-layer chromatography in all 49 cases; in 5 (10%) of cases, only traces were present.

In 3 cases, further characterization of the saturated hydrocarbons by mass spectrometry revealed a pattern typical for mineral oil, although the case histories did not indicate that mineral oil had been used by these 3 patients. The lymph nodes also contained traces of n-alkanes and monocycloalkanes, with higher molecular weights than are generally found in mineral oil, but no aromatic hydrocarbons were detected in the samples.

The authors felt that the high incidence of mineral oil droplets found in abdominal lymph nodes was out of proportion to laxative use and other medicinal uses of mineral oil. Non-medicinal sources of mineral oil ingestion (it was widely used in the food processing industry as of 1964) were thought to account for the above findings. In laxative doses, up to 2% of the ingested mineral oil may be absorbed. Processed foods containing mineral oil were calculated to add an additional ingestion of 47.5 grams of mineral oil, on the average, per capita per year to the American diet (28).

As in the abdominal lymph nodes, the authors were also able to identify saturated hydrocarbons of liquid oil droplets in 60 livers and 34 spleens obtained from 63 patients at autopsy (87).

In the spleens, oil vacuoles were extensive, most often located near the periphery of the splenic follicles and adjacent to trabeculae and blood vessels. In several specimens, collections of oil-containing vacuoles were seen beneath the endothelium of large veins. Although it was unclear whether the large droplets (100 μ in diameter) were intra- or extracellular, the smaller droplets were definitely within macrophages.

Hepatic collections of oil-filled vacuoles were mostly limited to the portal triads and areas of scarring, with a few instances of collections in the hepatic parenchyma (87).

Chemical determinations revealed mineral oil levels of 0.11-4.1 mg per gram of liver and 0.14-4.5 mg per gram of spleen. In 25 cadavers in which both the liver and spleen could be examined, there was good correlation between the liver and spleen mineral oil content per gram of tissue (87).

The liver and spleen oil content was concluded to be due to drainage of the abdominal lymph nodes via the hepatic system of lymphatics (87).

3. Metabolism

Not much is known about the ability of the organism to metabolize mineral oil, consisting of branched and cyclic alkanes. It is known that straight chain paraffins, such as octadecane, are oxidized to fatty acids in rat intestinal mucosa. An intestinal dehydrase removes hydrogen from the 1,2-position, followed by oxidation. The products of the reaction were recovered in intestinal lymph (118). Radioactive hexadecane was found to be oxidized in the microsomal fraction of guinea pig intestinal mucosa; cytochrome P_{450} was involved in the oxidation, which required NAD, NADP and glucose-6-phosphate (120). Goat and rat liver homogenates metabolized hexadecane, as did the microsomal fraction of mouse liver. Mouse lung microsomes were weak oxidizers of these paraffins, and kidney microsomes were inactive (126).

The aromatic components of lubricating oils may be metabolized in the liver. Hepatic monooxygenases convert naphthalene to naphthalene-1,2-oxide, which then either spontaneously isomerizes to 1-naphthol, is enzymatically hydrated to a trans-dihydrodiol, or conjugates both spontaneously and by enzymatic catalysis with glutathione. The conversion of polycyclic aromatic hydrocarbons to oxides of phenanthrene and benzanthracene also occurs. Glutathione conjugates are metabolized to mercapturic acids, for urinary excretion (128).

In vitro studies show that polycyclic aromatic hydrocarbons are metabolized into intermediate K-region epoxides, which are more active carcinogens than the parent compounds (18). The K-region is a particularly active site in a molecule having a high electron density, such as the 9,10-bond of phenanthrene. Microsomal enzymes convert phenanthrene, benzo(a)-anthracene, pyrene, benzo(a)pyrene, 7,12-dimethyl(a)anthracene and 3-methylcholanthrene into intermediate arene oxides (K-region epoxides) which are aromatic compounds in which a formal double bond has undergone epoxidation.

Arene oxides of benzpyrene were mutagenic in strains of *Salmonella typhimurium* and in Chinese hamster V79 cells, but the value of mutation experiments in determining carcinogenic activity of these epoxides was considered to be uncertain (132).

The epoxides are alkylating agents that bind with DNA and RNA, preferentially to adenine and guanine binding sites (18). The covalent bonding of these intermediates to intracellular macromolecules provides a molecular basis for the carcinogenicity of the polycyclic aromatic hydrocarbons (128, 133).

The enzyme (aryl hydrocarbon hydroxylase) which forms the epoxides is an inducible enzyme, under genetic control. Differences in susceptibility to carcinogenic effects of polycyclic aromatic hydrocarbons in experimental animals are highly correlated with the presence or absence of this genetically-mediated ability to induce the enzyme. In human tissues, aryl hydrocarbon hydroxylase activity has been found to be greater in smokers than in non-smokers, although a 70-fold variation in the activity of this enzyme was shown in smokers. Aryl hydrocarbon hydroxylase is found in human skin, and the possibility that skin cancer develops in oil-exposed individuals possessing a more inducible enzyme cannot be overlooked (18).

4. Excretion

The excretion of lubricating oil which is inhaled or aspirated into the lungs has not been studied. The oil droplets are formed into paraffinomas or captured in macrophages in the process of lipoid pneumonia. The pulmonary tissue reaction to mineral oil is to eliminate it, by expectoration in monocytes, removal by lymphatics or encystment by granulomas (71). When mineral oil is added to the lung in small quantities over long periods of time, as in chronic laxative ingestion and aspiration, it is not eliminated, but rather it accumulates as large deposits of oil in the lungs (68).

In humans, ingestion of mineral oil leads to excretion of 98% of the dose, unchanged in the feces (28). In Ebert's rats, fed a dose equivalent to the human recommended laxative dose, more than 80% of the mineral oil was excreted unchanged in feces (130). Twenty-four hours after the oral dosing (0.66 ml/kg of body weight of tritiated U.S.P. mineral oil), about 4.5% of the dose remained in the alimentary tract. By 48 hours, the amount of mineral oil remaining in the animal was about 1%, of which 0.7% was in the alimentary tract. Of the total dose, 0.1% remained in the animal after 21 days. Seven to 8% of the radioactivity administered in the single 0.66 ml/kg dose was excreted in the urine during the week following administration, and in the next week an additional 1-2% was collected. Less than 2% of the total urine radioactivity was extractable by toluene (mineral oil) - the amount of tritrated mineral oil in the urine varied between 0.3 and 2.5 µg/day ($0.3\text{-}2.5 \times 10^{-3}$% of the dose administered). The kidney was therefore only able to excrete trace quantities of the administered mineral oil, although the mineral oil was clearly demonstrated by chemical analysis of kidney homogenates (130).

VI. OCCUPATIONAL HEALTH AND SAFETY PRACTICES AND STANDARDS

The untoward effects of occupational exposure to SGF No. 1 fogs are largely unknown. Industrial practices are geared toward avoidance of exposure as a safeguard against dermatitis, since this has been the prevailing toxicological manifestation after occupational exposure to diesel fuel, heating oils and kerosene.

SGF No. 2, the lubricating oil fog, seems more dangerous due to its documented carcinogenicity for the skin of humans and animals. Pulmonary toxicity and carcinogenicity are not completely agreed upon in the current literature. In industrial practices, a limiting concentration for oil mist in workroom air has been established, and substitution of less carcinogenic oils may be practiced.

The two types of fog oil, SGF No. 1 and SGF No. 2, will be discussed separately in the remainder of this chapter.

A. SGF No. 1

Certain precautions for limiting exposure are reviewed. As new experimental data becomes available, appropriate revisions should be considered.

1. Standards

No standards for regulating occupational exposure to fogs, smokes, mists or fumes of middle distillate fuels (diesel fuel, fuel oil, kerosene) have been established to date.

2. Protective Measures

In fogging operations, inhalation of aerosol droplets of SGF No. 1 may be controlled by protective field masks utilizing activated charcoal filters, such as MIL-M-50079E(MU) (134). The fog concentration in the atmosphere, the amount of generator exhaust contained in the fog and the degree of thermal decomposition of the oil droplets making up the fog are unknown, as previously discussed in this report.

Control of skin contact with these fuels through the use of protective skin pastes or barrier creams, which may prevent absorption of the fuel, is recommended where occupational exposure to the liquid is a problem. Rao (50) described a silicone oil ointment which was found to be effective in controlling dermatitis, and was soothing and without untoward systemic effects. Ilkin et al. recommended the application of protective barrier creams prior to exposure, and the use of cleansing pastes at the end of the workday. Acceptable cleansers included: soap and lanolin; industrial or liquid soap; and lukewarm 0.25-0.5% ammonia solution (42).

Skin softeners may control the severity of dermatitis by helping to prevent abscess formation (42). A solution of equal parts of ethyl alcohol, glycerine, ammonia and water, and 0.5% chloramine in water was recommended.

Mechanical barriers, such as gloves and aprons, may be useful if they do not interfere with performance. Some authors maintain that the use of gloves contributes to sloppy personal hygiene, and that only scrupulous cleanliness and prophylactic measures can effectively control exposure to these fuels (49, 50). Others highly recommend protective clothing where practical (41, 135).

3. Medical Surveillance

Constitutional factors play an important role in individual susceptibility to irritation of the skin or mucous membranes. Dry, senile skin is sensitive to agents which may cause dermatitis. The skin of Caucasians is more sensitive to chemical irritants than the skin of Blacks (22). Some individuals may be occupationally exposed for years before developing dermatitis to these fuels.

Screening of all individuals prior to assignment to tasks in which they will be exposed to SGF No. 1 smoke is necessary in order to exclude persons with the following conditions: organic disease of the heart, lungs, kidneys or liver; history of allergy to hydrocarbons; chronic skin disease; hematologic abnormalities; and possibly a history of benzene intoxication. Gerarde (8) states that exposure to aromatic hydrocarbons or mixtures containing them must be avoided by these individuals.

Periodical medical examinations are essential for the early detection of dermatitis as well as possible inhalation effects of SGF No. 1 smoke. Documentation of exposure effects is necessary, in view of the limited information which now exists in this area.

4. Control Measures

In conditions where it is impossible to prevent exposure, personnel must be educated in the use of protective skin creams and clothing, the use of proper cleansers after exposure and the importance of cleanliness of work clothes. Early recognition of symptoms of respiratory, skin and other untoward reactions is essential, and requires periodical medical surveillance. Enforcement of safety and cleanliness regulations is equally essential.

Intravehicular exposures can be minimized by the use of activated charcoal filtering masks, or by filters covering ventilation intake ports. Precautions to exclude unfiltered air and smoke from the smoke-generating vehicle cabin, such as keeping windows closed, are necessary.

B. SGF No. 2

What clearly emerges after examining the epidemiology and toxicology of exposure to lubricating oil mist and oil, especially in industry, is the carcinogenic activity of oil components for the skin of animals and men. Falk summarized the situation in stating that the cancers most easily produced with polycyclic aromatic hydrocarbons found in unrefined lubricating oils, in

experimental species, have been squamous cell carcinomas, and the most frequent cancer observed in humans in association with occupational exposure to the oils in skin cancer. The difficulty in inducing pulmonary cancer in experimental animals, with polycyclic aromatic hydrocarbons, may reflect the low incidence of occupational lung cancer. Effective physiologic defenses are at work, possibly to prevent initiation of carcinogenic processes (66).

Standards for oil mist exposure, and methods of protection of military personnel are presented.

1. Standards

The U.S. Occupational Safety and Health Administration standard for exposure to oil mist in the air of industrial workplaces is 5 mg/m^3 (8 hr time-weighted average) (136).

According to reports of newspaper printing rooms, the oil mist was considered more of a nuisance than a health hazard. The workers wore white paper hats to protect their hair from the oil mist, and they were accustomed to blowing their noses into facial tissues which were stained black from the oil mist (mineral oil with suspended carbon blacks; newspaper ink) deposits in their noses. There had only been one compensation claim for a man with asthma of 44 years duration, and whose onset of asthma had occurred at age 14, prior to his employment in the newspaper printing occupation (24).

Hendricks also reported that, according to the Detroit Bureau of Industrial Hygiene, air sampling in plants had been prompted by worker complaints due to discomfort, but not due to health considerations. No lung difficulties in this sample of workers could be attributed to oil mist exposure. At oil mist concentrations in workroom air below 5 mg/m^3 there are few complaints among workers, while above 5 mg/m^3, the oil mist becomes visible in the air and discomfort is reported (57).

It is obvious that in fogging operations where SGF No. 2 is used, the intentionally dense oil mist which is kept hovering over entire armies must achieve atmospheric concentrations far greater than 5 mg/m^3. However, actual concentrations have not been reported in the available literature.

2. Protective Measures

Two ways to deal with the need to protect military personnel from cancer are avoidance of exposure, and removal of carcinogens from the oils with which these people must come into contact.

a. oil refining

Removal of polycyclic aromatic hydrocarbons from lubricating oils which are destined to be used in situations involving human exposure, is the most recommended and safest method of protecting humans from cancers due to oil exposure (18, 20, 59, 60, 62, 66, 76).

Originally, it was believed that sulfuric acid destroyed the carcinogenic substances in lubricating oil, e.g., benzo(a)pyrene. Then it was found that surfuric acid removed, rather than destroyed this chemical. Sulfuric acid treated oils were still carcinogenic in animals (62) and in humans (53, 63), especially in the Birmingham, England factories.

It has been possible to remove polycyclic aromatic hydrocarbons from lubricating oils, using extraction procedures with furfural, cresol or phenol (18, 62, 66). Solvent extraction creates a white oil. SGF No. 2, being straw colored (31), is probably not completely devoid of these carcinogenic aromatic compounds.

Some researchers have suggested the establishment of a threshold value for polycyclic aromatic hydrocarbons in refined lubricating oils intended for use in industry where occupational exposure is encountered (20).

However, according to Kipling, 1976, tests which might determine the total aromatic hydrocarbon content of oils or the concentration of single carcinogenic hydrocarbons are not reliable (18). Estimation of benzo(a)pyrene has been accomplished with ultraviolet absorption, but the method is not sufficiently accurate to be of value for routine work. Separation and X-ray fluorescence is another method (29). Until a simple and reliable test becomes generally available, there is no easy means of determining the polycyclic aromatic hydrocarbon concentration of solvent refined lubricating oils (18).

For medicinal mineral oil, sulfonation and processing are used for extraction of aromatic amines and unsaturated hydrocarbons from the finished product. This degree of purity is evidenced by absence of fluorescence under ultraviolet light (83). U.S.P. standards for medicinal mineral oil are discussed under Physical and Chemical Properties.

b. avoidance of exposure

In industry, protective aprons, hats, overalls, gloves, etc. are sometimes provided, or else suggested to reduce the amount of oil contact of the worker's skin (18, 60, 76).

The use of skin cleansers after exposure to lubricating oils is encouraged, and the importance of washing off the oil is undisputed (18, 66, 75). However, in a 1952 study using fluorescent oils, 28 varieties of cleansers, including household and industrial soaps, detergents and formulas, were found to be ineffective in removing all of the oil from the skin of human volunteers. After applying the fluorescent oil, and washing with the cleansers, the skin still fluoresced in the area on which oil had been applied (64).

Protective lotions and other formulations, when applied to the skin prior to exposure, may reduce the occurrence of dermatitis in individuals with sensitive skin. However, one author's opinion is notable. Eckhardt emphasized the positive value of a soap and water wash, stating that protective creams have no demonstrated value against carcinogenic agents, but they have a psychological effect in that they encourage the individual to wash after work (18).

3. Medical Surveillance

In industry, regular medical examinations - every 6 months - should be required, due to the cancer risk of occupational exposure to unrefined lubricating oils (18, 60).

In addition, workers should be instructed on methods of self examination of the skin and scrotum, and skin changes should be reported to plant health supervisors, so that early premalignant conditions can be immediately dealt with (18, 60).

Regardless of the length of exposure to SGF No. 2 oil smoke, all involved personnel should be checked for respiratory and skin conditions which could develop, and adequate medical documentation of adverse effects should be undertaken.

In view of the fact that about thirty years have passed since the smoke screening operations of World War II, in Anzio, Northern Europe and other locations, armed forces personnel involved in that exposure should be traced in order to assess morbidity and mortality trends, especially with respect to cancer mortality.

VII. METHODS OF SAMPLING AND ANALYSIS

Because of the differences in physical and chemical properties between fuels (SGF NO. 1) and lubricants (SGF No. 2), collection and analytic techniques may also vary. The two types of fog oil, SGF No. 1 and SGF No. 2, will therefore be reviewed separately in this chapter.

A. SGF No. 1

Sampling in air, and analysis in biologic media are given for middle distillate fuels and their fogs. These methods should be applicable to SGF No. 1

1. Atmospheric sampling

A Mine Safety Appliances 60-25 Electrostatic Sampler was used, operating at 18 1/min for 30 min; before and after the sampling period the precipitator tube was weighed to determine the weight of material collected (105).

A special grade of paper (S & S 2045 BM) was used to absorb the hydrocarbon droplets in the air drawn through it (137).

An acidic potassium dichromate solution was used to bathe the sample, but it was not clear if vapors only, or also aerosols, would be absorbed (138). Vapors would interfere with aerosol determination.

Fiberglass filter paper was used to adsorb the droplets from the sample; portable apparatus, for personal use, was as suitable as larger equipment intended for room averaging. At an expected value of 5 mg/m^3, the air is drawn at 2 1/min for 10 min through a 25 or 37 mm filter for personal sampling - 100 min for 0.5 mg/m^3 (139).

2. Analysis of air samples

A microscope-photometer arrangement was used to determine increase in translucence of chromatographic grade paper through which the sample had been drawn (137).

Ol'khovskaya (138) measured the change in color of a 0.01% solution of potassium dichromate in concentrated sulfuric acid (through which the sample had been drawn); sensitivity was 20 µg/3 ml reagent for kerosene when a 1.5-1 air sample was used; wavelength monitored was not given.

The Institute of Petroleum Occupational Hygiene Subcommittee (139) review of accepted methods only commented on one sampling technique, but discussed three ways of determining amount collected. A gravimetric method involved solvent extraction of the filter, evaporation and weighing; its sensitivity was 0.1 mg. A drawback was possible loss of volatiles during the solvent removal step. Extraction of the filter and

measurement of the UV absorbance at 200-300 nm was useful if a known was available to prepare a calibration curve; the sensitivity was 0.1 mg when the curve had unit slope. Alternatively, the IR absorbance of the extract in the 3.4 μ region could be checked against a standard; sensitivity was 0.05 mg.

3. Biologic media

A technique for blood kerosene is suitable when an original sample is available to calibrate the method. Five ml of blood is hemolyzed in dilute hydrochloric acid, then extracted with carbon tetrachloride. The extract is mixed with a formaldehyde-sulfuric acid reagent (which reacts with aromatics) and the color produced measured at 490 nm in a colorimeter. The method was good to a lower limit of 10 ppm when 14% aromatics were present (140).

B. SGF No. 2

Atmospheric sampling methods are designed either to simply collect or collect and classify lubricating oil mists according to droplet size. After sampling, the collected oil can be weighed, or weight can be determined indirectly by spectrometric or chemical procedures. Mineral oils can be determined in biologic samples after differentiation from animal and vegetable fats and oils.

1. Atmospheric sampling

Electrostatic precipitators, inertial separators (compactors and impingers), gas washing bottles, evacuated gas pipettes, and filter media are discussed.

a. electrostatic precipitator tubes

This device draws a given volume of air per minute into an electrically charged collection tube. Wagner et al. (27, 105) used a collection rate of 8.2 liters per minute for 15 minutes. Concentrations less than 1 mg/m^3 were sampled efficiently, although a large sample was needed for accuracy. The maximum quantity of sample was limited to 20 mg to prevent loss of the sample by dripping of collected oil from the tube. Laboratory tests of precipitator efficiency, while incomplete, indicated that efficiency was adequate at air flows up to 325 liters per minute at a collecting potential of 11 kilovolts. A weight change of 1 mg or more was sufficient to provide acceptable accuracy for low oil mist concentrations (61).

b. filter media

Oil is collected by drawing a given volume of air per minute through a conditioned preweighed filter which captures the aerosol particles. Glass fiber filters were preferred to paper filters such as Whatman No. 41 or Knowlton grade 100 (57). Hervin and Lucas (55) collected workroom air on preweighed Gelman Type A (no organic binder) glass filters. Ely used a

BM-2133 filter with a high-volume air pump (74). Glass fiber filters require a large air sample for accuracy. A sampling rate of 15-25 liters per minute or less was recommended for a 1-inch glass filter (61). Cellulose ester filters were not recommended because they tended to clog with oil too rapidly and presented difficulties in obtaining reproducible tare weights (61). Glass fiber filters were used to detect atmospheric oil aerosol concentrations less than 1 mg/m^3. GF/A Whatman glass fiber filters do not collect vapors, according to Turner et al. (139), who used a sampling rate of 5-30 liters per minute with a commercial air pump. Personal sampler pumps usually operate at 2 liters per minute. Where oil mist concentrations are low (1 mg/m^3) Turner recommended operating general and personal samplers for not less than 1 hour, although higher oil mist concentrations can generally be measured in less time, e.g. 10 mg/m^3 concentrations can be sampled in 1 minute at 10 liters per minute and in 5 minutes at a rate of 2 liters per minute. Other satisfactory filter materials have been reported (74, 141, 142).

c. inertial separators

Cascade impactors and cyclone impingers collect and classify oil particles by their diameter. Goldstein (24) used this method to collect oil mists in newspaper pressrooms. Shoshkes (69) used the cascade impactor, with dry film slides, in conjunction with an air flow rate of 17.5 liters per minute, and backed by 2 glass wool filters. No detectable oil was found in the second filter. The cascade impactors require a collecting surface which can hold 1 mg or more of liquid. A flow of 20 liters per minute was a practical maximum rate for commercial impactors, with a minimum sampling time of 30-60 minutes. Disadvantages of cascade impactors include the possibility of significant loss of oil to the walls of the device, of coalescence of droplets and the necessity of long sampling times (61). Hendricks used a methyl ethyl ketone collection medium in a midget (personal) impinger (57).

d. gas washing bottles

In this method, a pump draws air at 1 liter per minute into gas washing bottles containing a solvent--tetrachloroethylene (54) or spectrograde carbon tetrachloride (74). In the former setup, three bottles were connected in series, and 20 liters of air were sampled, the sensitivity being 10 mg of oil per m^3 of air.

e. evacuated gas pipettes

This method does not exclude sampling of vapors of oil or other organic substances present in workroom air. These substances would falsify the determination of concentration (142).

f. chromatographic grade paper

Air containing oil mist was drawn through chromatographic grade filter paper. A microscope-photometer arrangement was then used to determine the increase in translucency of the paper containing the oil. The room air oil

mist concentration was determined from the degree of translucency (137). The sensitivity of this method was not reported.

2. Analysis of air samples

a. gravimetry

The method consists of drawing air at a well defined rate through a pre-weighed filter and recording the weight gain after a measured volume of air has been sampled. The oil may be extracted from the filter with a low-boiling solvent, followed by drying and weighing (57, 74, 105, 139). Using Gelman Type A filters, the minimum gravimetrically detectable level was 0.1 mg of oil (55).

b. ultraviolet absorption

Oil was extracted from the collecting filter using a low boiling solvent. The extract was placed in a 40 mm pathlength silica cell, and ultraviolet absorbance was read at 300-200 nm. Peak absorbance of the extract was compared with a calibration curve to determine the weight of oil collected. Oil content as low as 0.1 mg was readily detected by this method, and there was excellent correlation between the gravimetric and ultraviolet determination (139).

c. infrared absorption

Oil concentration was measured by infrared absorption by transferring a solvent extracted oil sample to 4 cm cuvettes, and using a double beam infrared spectrophotometer in the 3.4 nm region to measure C-H stretching bands. The results were compared with blank determinations and with a carbon tetrachloride comparitor cell. The absolute sensitivity of this method was 0.05 mg of oil (139). Hervin and Lucas (55) reported a minimum detection level of 0.001 mg for mineral oil mists.

Using tetrachloroethylene as a solvent, samples obtained from gas washing bottles were determined to a sensitivity of 0.2 mg of oil, using 10 mm-thickness cuvettes. Extinction was linear in the range of 1-10 mg of oil per 25 ml of tetrachloroethylene, and values falling outside the curve were extrapolated (54).

d. colorimetry

The sample was extracted with carbon tetrachloride from film slides and glass wool filters (from cascade impactor sampling). Calco Oil Blue 2A dye was dissolved to saturation in the oil samples and the concentration of dissolved dye was read in a spectrophotometer. A known quantity of dyed oil dissolved in carbon tetrachloride was used as a standard (69).

e. emulsion method

Oil collected on filters and in evacuated gas pipettes was diluted in glacial acetic acid and water, forming an emulsion, from which the quantity

of oil was determined. Sensitivity was 0.05 mg in a 5 ml sample volume for most mineral oils (142).

f. calculation of oil mist concentration

$$\text{Concentration of oil mist} = \frac{\text{mg oil found x 1000}}{\text{liters of air sampled}} \quad \text{mg/m}^3.$$

This equation converts the weight of oil determined in the oil sample into units used in industrial limiting standards, namely milligrams of oil per cubic meter of air (139).

3. Sampling methods for determination of droplet size

a. sampling for optical microscope

In one animal study, particle size was determined using a glass microscope slide placed on the floor of an animal exposure chamber for a few minutes to obtain a sample of droplets by settling. It was necessary to cover the slide with 5 layers of monomolecular films of barium stearate to prevent the drops from spreading over the surface of the slide into a continuous film of oil (143).

Settling methods, however, were considered unacceptable because only the larger diameter droplets are deposited while the smaller ones remain airborne (57). Collection was more accurately accomplished by mounting a glass slide onto the head of an electrostatic precipitator (27, 57, 61). A thermal precipitator was used in conjunction with glass slides (61). The concentration of the sample must be small enough that the droplets do not run together or spread into a film (61).

After the microscopic slide collection, particle diameters were measured with a micrometer (61), or an eyepiece graticule in a bright field microscope equipped with a 10X eyepiece and a 43X objective (27, 105). If microscopic sizing can be done within 2 hours of sampling, and when more samples can be taken if the first proves unsatisfactory, microscopic examination can give information regarding the nature of particulates other than oil which may be present in the air sample. But even with such non-volatile oils as U.S.P. light mineral oil, a sample will evaporate from the slide if it is left standing for a long time (1 1/2 hours). With optical microscopic size determination, small droplets are often difficult to resolve, while large droplets tend to spread out on the slide (61).

In one study, glass slides were photographed under the microscope immediately after sampling, and the photographs were used to measure diameters. Particles with diameters greater than 1 μ could be detected (54).

b. photometry

Rapid automatic single particle sizing light-scattering photometers are, in Ayer's opinion, the only fast and convenient method for determining droplet size. Droplets are sized and counted while airborne, and the droplets

are directly comparable to spheres with which the instrument is calibrated. The limitation on maximum concentration is 3500 droplets per ml which are greater than 0.3 μ in diameter (61). Wagner determined particle size with the aerosol photometer, and confirmed the results with a microscopic optical method (105).

c. inertial separators

Both the cascade impactor and cyclone impinger collect and classify oil droplets by their diameters (61). Disadvantages include the possibility of significant wall losses, of coalescence of droplets in the sampler and the necessity of long sampling times (61). Miniature cyclone pre-samplers (personal models) tended to retain particles larger than an empirically determined size which is dependent upon air flow rate and the properties of the material being collected. These devices allow passage of smaller particles to a second stage filter. By removing larger droplets, it is possible to estimate the amount of material which might be expected to penetrate deep into the lungs (61).

Cascade impactors require a collecting surface which can hold 1 mg or more of liquid. A practical maximal flow rate of 20 liters per minute for a minimum of 30-60 minutes was recommended for commercial impactors (61).

d. the Millikan oil drop apparatus

Oil droplet size was measured using Millikan oil drop apparatus, in which the rate of fall of droplets in the air was determined, and the droplet radius was then calculated using the formula:

$$r = 9.11\sqrt{\frac{v}{e\left(1 + \frac{0.09}{r}\right)}}$$

where r = radius of oil droplet in microns, v = rate of fall of the droplet in cm/sec, and e = density of the oil. The factor $1 + \frac{0.09}{r}$ resulted from the Cunningham-Millikan correction which should be used for droplets smaller than 10^{-4} cm (104).

4. Biologic media

Histochemical staining techniques are useful in the detection of medicinal mineral oil (100% saturated hydrocarbons) and possibly lubricating oil in sputum and pulmonary tissue samples; the applicability of these methods lies in the diagnosis of pneumonia due to ingestion and aspiration of mineral oils. Analytic methods for lipid extracts in biologic tissues are often not specific for mineral oil, with the exception of column and thin-layer chromatography. Thin layer chromatography has also been used in the detection of mineral oil adulterants in edible cooking oil.

a. histochemical stains

Specific identification of mineral oil in tissues requires the isolation

and structural characterization of the saturated hydrocarbons in the tissue. Mere demonstration of the presence of large amounts of saturated hydrocarbons in tissues is, however, sufficient proof of the presence of mineral oil in most cases, because endogenous lipids can be excluded by virtue of their unsaturated hydrocarbon content, as can fats and oils in food products (86).

In tissues containing readily microsopically visible oil droplets, a dye which stains most oily or fatty substances can be applied to the fixed tissue. Oil red O, Sudan III and Sudan IV all stain oil droplets red or orange (68, 79, 82, 88, 104). Mineral oil tends to stain less intensely than other lipids (86). If further differentiation is desired, a second step is added. A dye is applied which stains most tissue lipids but does not stain mineral oil. Osmic acid (68), osmium tetroxide or Sudan Black B (86) will stain unsaturated lipids black, while saturated oil droplets remain red. However, failure to stain is not unique to saturated hydrocarbons. Another drawback is that positive staining with osmium does not rule out the presence of saturated hydrocarbons (86).

Mineral oil and motor oil droplets larger than 1-2 μ in diameter were visualized as light gray, translucent droplets against a dark background of lung parenchyma, after staining the slide with osmic acid alone (69). Sudan Black B alone stained mineral oil faintly violet, while heavily staining most other tissue lipids (86). Clear oil droplets smaller than 1 μ in diameter could not be detected (69).

Casey (82) demonstrated oil in pulmonary tissue from a case of lipid pneumonia by the Sudan IV stain. Cross-prism microscopy and special stains (not identified or described) indicated that the material was mineral oil and not of animal or vegetable origin.

Sputum lipid analysis can be useful in diagnosing mineral oil pneumonia (70, 79, 88). Sudan III is not specific, due to interference from fat in food particles in the sputum. Microscopic lipid is also present in the sputum of healthy individuals, predominantly embedded in mucin (79).

b. extraction of oil

Unfixed fresh or frozen tissue was saponified with a solution of KOH, water and isopropanol. The upper phase of the resulting two-phase system was dried, and saturated hydrocarbons were separated from other lipids by column chromatography, using molecular sieve adsorption with crystalline zeolites to retain n-alkanes and exclude branched and cyclic alkanes (87).

Lipid extraction from tissues can also be accomplished in chloroform-methanol, 2:1 (86).

c. analysis of oil extracts

Analytic methods for lipids extracted from biologic media are often not specific for saturated hydrocarbons (86). These techniques include:

1. Gravimetric determination of non-cholesterol, non-saponifiable lipids, and comparison with control tissue extracts - This method can reveal excess saturated hydrocarbons, but it is not specific for mineral oil (86).

2. Infrared spectrometry of tissue lipids - This method is not specific, because although mineral oil has a characteristic absorption band at 727 nm, other unsaturates and organic compounds also have this absorption band (86).

3. Ultraviolet spectrometry - This method is not valid, because saturated hydrocarbons have no significant light absorption in the ultraviolet range. Ultraviolet absorption by commercial mineral oils must be due to the presence of contaminants (86).

4. Column chromatography - Using this technique, a reasonably specific separation of saturated hydrocarbons from other tissue lipids can be accomplished (86).

5. Thin-layer chromatography - This is simpler and less time consuming than column chromatography, and allows a roughly quantitative isolation of saturated hydrocarbons of mineral oil origin from biologic media (86).

Lipids extracted from human tissues in chloroform-methanol, 2:1, were applied in benzene onto 20 x 20-cm glass plates with silica gel and calcium sulfate binder. As little as 0.5 µg of saturated hydrocarbon, and up to about 500 µg could be detected, by developing the plates (10 cm, 20-30 min) with n-hexane, spraying with 50% H_2SO_4, and charring in an oven (15 min, 170°C). This method charred branched and cyclic alkanes but not n-alkanes. Another detection method called for spraying the plates with 0.025%, w/v, rhodamine-6-G in acetone, air drying, spraying with 0.025% w/v, rhodamine-6-G in water, and examining the wet plates under ultraviolet light. All saturated hydrocarbons were dark or brightly fluorescent yellow spots.

Spot size and intensity were proportional to the quantity of saturated hydrocarbons applied, and quantitative estimates were made by comparison with standard quantities of reference lipids included on the same plate (86).

Thin-layer chromatography of sputum lipids of patients presumed to be suffering from mineral oil pneumonia can be diagnostic (79).

In one case of mineral oil pneumonia, thin-layer chromatography of tissue from the lungs and hilar lymph nodes showed a high concentration of saturated hydrocarbons considered to be virtually specific for mineral oil (67).

5. Analysis of mineral oil in edible oils

Adulteration of widely used vegetable oils (castor oil, coconut oil, sesame oil, etc.) with inexpensive mineral oil was detected by thin-layer chromatography, in quantities up to 3% mineral oil. Silica gel G plates

(20 x 20-cm, 250-μ layers) were dried, sprayed with silver nitrate in aqueous ethanol, redried, and cooled. Spots of oil samples in chloroform (1% solution) were applied and eluted in benzene (13.7 cm, 30 min). The plates were oven dried, sprayed with 50% ethanolic phosphoric acid and charred.

Liquid paraffin and transformer oil spots migrated further than pure vegetable oil spots. In the vegetable oils containing 3% liquid paraffin, the mineral oil appeared as a distinct spot which migrated further than the rest of the oil sample. Tallow, an animal fat, migrated at approximately the same speed as the vegetable oils (144).

VIII. TECHNICAL SUMMARY

The scope of this problem definition study encompasses the physico-chemical, toxicological and occupational health aspects of two major types of petroleum products, fuels and lubricants, of which the two fog oils, smoke generating fog (SGF) oil No. 1 and SGF No. 2, are representatives, respectively. Due to the fact that differences between the two fog oils are of a greater significance than their similarities, it is necessary to consider them separately in discussing their biomedical and physico-chemical properties. The literature on SGF No. 1 and No. 2 themselves is scanty in all areas. Research into the toxicological aspects of fuels and lubricants is only slightly greater in volume, offering at least a starting point upon which to base future investigations. Nevertheless, some important statements have been based upon this small amount of research. This chapter presents, in condensed form, the reviewed literature on SGF No. 1 and related fuels, and on SGF No. 2 and related lubricants, both products of the petroleum industry.

A. Physical and Chemical Properties of Fog Oils SGF No. 1 and SGF No. 2

SGF No. 1 is a petroleum product which corresponds in boiling range and other properties to the middle distillate fuels, lighter grade diesel fuel and fuel oils #1 and 2. Therefore, the distribution of hydrocarbon types and molecular weights of SGF No. 1 should also correspond to these fuels, and they should be toxicologically similar. In fact, an order for SGF No. 1 would probably be drawn from stocks destined to be one of these fuels. Likewise, SGF No. 2 is drawn from a lubricant oil stock also sold as a raw material to various industries. The physical and chemical properties, human and animal toxicity, pharmacokinetics and occupational health and safety aspects are presented for SGF No. 1 or SGF No. 2 where possible, and for SGF NO. 1 or No. 2 models, i.e. other fuels or lubricants in the same respective classes, where information on the fog oils is lacking.

1. SGF No. 1

The Military Specification for SGF No. 1 fog oil (MIL-F-12070A, 10 May 1956) requires it to have a boiling range characteristic of other middle distillate fuels, as well as meeting a maximum carbon residue, pour point, neutralization number and viscosity. In the research of Lushbaugh et al., in the 1940's, SGF No. 1 was described as a dark colored and highly fluorescent liquid. The Military Specification further requires that it is free of any additives.

SGF No. 1 fog oil is produced from crude oil by fractional distillation; it boils in approximately the same range as other middle distillate fuels, such as fuel oils #1 and 2, and light grade diesel fuel, that is, 390-610°F (200-320°C). Refinery procedures such as catalytic and thermal cracking and related operations, which are used to convert crude oil fractions of lower economic value (gases, residues) to oils richer in gasoline fractions, give off a cracked middle distillate as a by-product. This cracked material may be blended with middle distillates produced directly from crude oil (straight run), in any proportion, provided that the end product is a fuel meeting the SGF No. 1 requirements. Further processing of SGF No. 1 and related middle distillates

includes deasphalting and other procedures which extract various compounds from the fuel, such as wax, resinous materials, sulfur and heavy metals. Kerosene is produced by extraction of aromatic hydrocarbons from this fuel.

The middle distillate fuels which leave the refinery are composed of a wide variety of hydrocarbon compounds: paraffins, cycloparaffins, aromatic hydrocarbons and olefins, ranging in carbon number from C_9 to C_{20}. The actual percentages of these types of hydrocarbons in a given fuel sample are a reflection of the composition of the crude oil from which it was distilled, as well as refining techniques. Hydrocarbon types present in middle distillates may include: normal and isoparaffins, mono-, di- and tricycloparaffins, alkylbenzenes, indanes, tetralins, dihydronaphthalenes, alkylnaphthalenes, acenaphthalenes, acenaphthylenes, fluorenes, anthracenes, phenanthrenes, and olefins.

The complexity of the mixture which is SGF No. 1 is readily apparent. It is an even more difficult task to evaluate SGF No. 1 in terms of toxicity, because individual components of the mixture may have effects on the body which are masked or accentuated by interaction with other fuel components. Due to the wide variation of composition of different batches of SGF No. 1, effects on the organism may also depend upon the particular batch of the oil which is being tested.

2. SGF No. 2

According to communications with U.S. Army representatives of Shell Oil Company (Houston, Texas), SGF No. 2 is a lubricating oil. The Military Specification, MIL-F-12070A, May 10, 1956, requires this oil to have a specific viscosity, as well as limiting carbon residue, neutralization number, flash point, and pour point. The term "100 pale oil" has been used to characterize the substance: 100 refers to the viscosity, i.e. 100-110 Saybolt Universal Units at 100°F; pale refers to the fact that it is a pale or straw-colored liquid. The oil must be free of additives.

Lubricating oils are generally distilled from crude petroleum under reduced pressure, in order to avoid thermal decomposition of the oil, which would result in inferior lubricating properties. Lubricating oils, including SGF No. 2, may undergo further treatment to remove sulfur, heavy metals, resinous materials and some polycyclic aromatic hydrocarbons and paraffinic waxes.

The same lubricating oil which is sold as SGF No. 2 may be utilized as a raw oil in manufacturing industrial cutting, metalworking, lubricating and cooling oils. It may be used as a vehicle for spraying livestock and agriculture with various chemicals. Or, it may be further refined into a white oil, which is used in newspaper ink, in industrial applications where less refined oils are prohibited, and in the manufacture of medicinal mineral oils used for laxative, adjuvant or nose drop formulations.

Lubricating oils generally have a boiling range of 700-900°F (370-480°C), and contain hydrocarbons with 20-50 carbon atoms, in the molecular weight range of 240-420 atomic units. Hydrocarbons present include no more

than 10% alkanes, with cycloparaffins and aromatic hydrocarbons accounting for the remainder. Cycloparaffins with up to four cyclopentane or cyclohexane rings per molecule predominate. Polycyclic aromatic hydrocarbons with 3 to 6 benzene rings, and as much as 160 µg/l benzo(a)pyrene have been identified in lubricating oils. Solvent extraction removes most aromatic hydrocarbons, creating white oils composed mainly of cycloparaffins with up to six rings per molecule. Synonyms for white mineral oil include U.S.P. mineral oil, liquid petrolatum and liquid paraffin.

B. Generation of Smoke from Fog Oils

Fog oil smoke is generated by a process of vaporization of the oil, followed by forcing the vapors out into the atmosphere; as the vaporized material meets the atmosphere, it is immediately condensed into a dry smoke, which consists of microdroplets of oil. The latest smoke generator, the M3A3, consumes 150 liters of fog oil an hour, producing a continuous smoke screen. The generator itself is a pulse-jet engine which consumes 11 1/2 liters of gasoline per hour. The concentration of oil droplets in the atmosphere which is required for this dense smoke is unknown.

The temperature required to vaporize the oil in the generator may or may not cause thermal breakdown of the oil, leading to the formation of even more hydrocarbon types. Analyses of fog oil smoke are not reported in the literature.

In the M3A3 smoke generator, exhaust vapors from the engine will mix with the vaporized fog oil and both are emitted together. The concentration of gasoline engine vapors in fog oil smoke is not reported. Effects of the mixture of fog oil and gasoline engine exhaust have not been studied.

The smoke is a stable dispersion of oil droplets with light-scattering properties. It settles very slowly, remaining afloat for around one hour. Meteorological conditions determine its range of ground coverage; the smoke may be carried as far as 6.5 kilometers from its point of generation.

C. Human Toxicity

Medical records from World War II reportedly revealed no indications that smoke generator unit personnel, or armies living in constant smoke screens for weeks on end, experienced any illness or carcinogenic or mutagenic effects related to exposure to fog oil smoke screens. There was no indication that precautions had been taken to avoid exposure. The documentation and medical follow-up of these exposed personnel was probably inadequate, according to the Edgewood Arsenal Toxicology Division of the U.S. Army.

Due to the problem of insufficient data, the toxicity of SGF No. 1, a fuel, and SGF No. 2, a lubricant, are discussed as representatives of the larger petroleum classes to which they belong, termed "models".

1. SGF No. 1 and Model Fuels

Acute and chronic toxicity of middle distillate fuels (lighter grades of diesel fuel, fuel oils No. 1 and No. 2, and kerosene) in humans are discussed.

a. acute toxicity

Normal subjects exposed to diesel fuel aerosols in concentrations as high as 300 mg/m^3 for 10 minutes experienced practically no eye nose or throat irritation. Exposures to deodorized kerosene vapors or aerosols, for 15 minutes, in concentrations up to 140 mg/m^3, caused no irritation or discomfort of the eye, nose or throat of the volunteers.

Acute skin contact with kerosene soaked clothing caused severe epidermal necrolysis in a 12-year-old boy. Extensive erythema and detachment of epidermal tissue overlying a purulent exudate occurred. Skin patch tests with kerosene for 24 hours caused skin irritations of varying degree in humans. Cycloparaffin-rich kerosene more frequently produced positive skin reactions after 24 hours, and a highly aromatic middle distillate fuel produced the strongest skin irritation. Pure aromatic hydrocarbons, such as monomethylated naphthalenes, a component of these fuels, produce slight skin reactions in persons undergoing 24-hour patch testing. Tetramethyl benzenes cause dehydration and defatting of the skin.

A worker who swallowed fuel oil during a siphoning procedure developed acute gastritis with hematemesis. Gastric mucosal lesions, observed on X-ray, healed in about 1 1/2 months. No systemic involvement was noted. Intense gastrointestinal irritation has been noted after kerosene swallowing.

Diesel fuel ingestion by young children often causes pneumonia, due to entry of the fuel into the lungs i.e., aspiration pneumonitis. Cough, dyspnea and a blood-tinged frothy discharge have been noted in these cases. Extensive bilateral pulmonary necrosis and gangrene occurred in a 44-year-old man who aspirated diesel fuel.

b. chronic toxicity

Chronic dermatitis due to repeated exposures to diesel fuel is dependent upon occupational and personal hygiene, individual skin sensitivity and other constitutional and environmental factors. Folliculitis, furuncles, pyoderma, abscesses and papular eruptions have been reported in the literature. The relationship between blood group (ABO system) and occurrence of dermatitis was studied in 25 workers; the conclusion was that blood grouping could provide a rough screening test for dermatitis for prospective employees working around fuel oils. Black persons and people with oily skin seem better able to resist fuel oil chronic dermatitis than persons with dry, senile or eczematous skin.

No other chronic effects have been documented in the literature.

2. SGF No. 2 and Lubricating Oils

Acute and chronic toxicity of petroleum lubricating oils (automotive, industrial and medicinal) in humans are presented.

a. acute toxicity

No appreciable eye, nose or throat irritation was reported following the exposure of 7 healthy subjects to up to 40 mg/m^3 of fresh automotive lubricating oil aerosol for a period of 10 minutes. There are no other reports of acute exposure toxicity in the literature.

b. chronic toxicity

Long-term exposure to oil mists occurs in many industrial settings, such as cotton spinning, newspaper printing, metalworking and steel, brass and aluminum manufacturing. In metalworking shops, lubricating oil mist concentrations up to 402 mg/m^3 have been reported. The low limit of visibility of oil mists is about 5 mg/m^3. The dense smokes generated for screening military personnel are probably more concentrated, although actual measurements of concentrations have not been made.

The oil mists found in industrial workplaces are generated by vaporization and rapid cooling into droplets of oil. In this case, the heat source for vaporization is the high-temperature zone of contact between the particular tool and the workpiece.

Chronic skin exposure to these oils occurs in the same setting, due to splashing of lubricating oils from machinery onto any part of the body, such as the face, arms and groin.

(1). carcinogenicity

Squamous cell carcinoma of the hands, face and groin (scrotum, vulva) after chronic oil exposure in industry has an occurrence which parallels the degree of refining an oil underwent prior to use. The polycyclic aromatic hydrocarbons present in all but white oils are probably responsible for their carcinogenicity. These are weak carcinogens (with the exception of benzo(a)pyrene).

Cases of skin cancer due to petroleum oils used in industries such as cotton mule spinning and metalworking reached a peak in 1928 and declined slowly by 1945, due to the introduction of concentrated sulfuric acid washing in the 1930's (to remove benzo(a)pyrene) and later on, solvent extraction of other polycyclic aromatic hydrocarbons from these oils.

Cases of skin cancer due to occupational oil exposure have been less numerous in the United States, Canada, Norway and Sweden than in the United Kingdom. In Holland, no skin cancers have been reported, and in Australia, the disease is rare among oil exposed workers (18).

In Birmingham, the industrial engineering center of the United Kingdom, skin cancer studies have revealed that over 86% of skin cancer cases that could be traced had been found to occur in association with oil exposure, although the type of oil used could not be related to incidence. Machine operators and tool setters had a significantly greater occurrence of second primaries of the skin, respiratory tract and larynx than the general population of this area.

In one region of France employing 5,000 workers who are exposed to lubricating oils and oil aerosols, 63% of 133 squamous cell carcinoma cases from 1960-1974 were of the scrotum, 30% of the arms or hands, and the remainder were of the face and neck. The scrotal cancer rate was 25 per 100,000, which was 36 times higher than the scrotal cancer rate of the general unexposed population of that area. Risk factors were psychological, social and constitutional, as well as occupational oil exposure and degree of personal and occupational hygiene.

Most men affected with scrotal cancer in the general population are over 70 years old, and it is considered a very rare disease. Oil-exposed men in metalworking, cotton and jute industries who develop scrotal cancer are in the 40-50 year age group and have had more than 6 years of oil exposure.

Digestive tract cancer mortality among oil-exposed workers in the United States is within the limits of the expected cancer rates for unexposed white males. Death rates for specific digestive organs were not examined.

Studies in Birmingham showed the larynx to be a site of excessive second primaries in occupationally exposed workers. Excess second primary tumors of the lip and stomach were also noted in occupationally exposed men with scrotal cancer. Because these cancers were manifested in only a small subset of the oil-exposed population, other factors may have been responsible for the enhanced susceptibility to cancer within this group.

Pulmonary tumor deaths due to inhalation of industrial oil mists are no greater than for the unexposed populations. Cancer mortality patterns in over 5,000 white males employed in metalworking for at least one year between 1938 and 1967 did not show any exposure-response relationship or latency effect to oil mist exposure. In some studies, higher bronchial cancer mortality rates have been reported, but the results are questionable due to comparisons with non-age-matched, unexposed populations. The few reports of bronchogenic carcinoma in oil-exposed workers have failed to consider smoking history and other possible etiologic agents.

Second primary tumors of the bronchus in men in Birmingham with scrotal cancer due to industrial oil exposure were excessive for men in some oily jobs but not others, leading to the conclusion that other factors, such as cigarette smoking and the wide prevalence of chronic bronchitis in England may be involved in this selected group.

The basis for enhanced susceptibility of some oil-exposed populations or individuals may be a constitutional, genetically controlled difference in ability of human tissues to metabolize the polycyclic aromatic hydrocarbons present in petroleum lubricating oils. The metabolites, called K-region epoxides, may be more carcinogenic than their parent compounds. The enzyme responsible for epoxide formation, aryl hydrocarbon hydroxylase, is an inducible enzyme present in human skin and other tissues, and its activity is genetically controlled, i.e., the enzyme is more inducible in some individuals than in others. Persons with a more inducible enzyme may be those with an enhanced susceptibility to tumors from chronic oil exposure.

(2). dermatotoxicity

Oil folliculitis, acne, eczema, contact sensitivity, as well as warts, rodent ulcers and premalignant skin conditions (pigmentary changes, atrophy, hyperkeratosis, telangectasia) have been reported due to chronic exposure to lubricating oils. The back of hands, forearms and groin are often affected. Oil acne was found to affect as many as 80% of automatic metal machine workers in Britain.

The lubricating oils break down the protective defenses of the skin. The skin barrier varies in thickness, and oils have less difficulty penetrating thin scrotal skin than the thick skin of the palms of the hands. Eczemas, inflammations and other conditions occur once the barrier is penetrated. Integrity of the skin barrier also depends upon moisture content and other constitutional factors. Friction of clothing against oil contaminated skin, as well as poor occupational and personal hygiene, contribute to dermatoses.

Skin patch tests with lubricating oils generally provoked minimal or negative skin reactions in 24 hours. Black persons were less sensitive to the oils than whites. Over 50% of white persons with eczemas of any etiology had mild skin reactions, while those with healthy skins had about 10% positive skin reactions.

(3). other toxic effects

No information is available on the effects of lubricating oils or mists upon the nervous system, cardiovascular system, blood or blood forming organs, liver, kidney and urogenital system, fertility, reproduction, growth or behavior.

(4). general mortality

In a study in which 778 newspaper pressmen (exposed to oil mists from printing ink) were compared with 1,207 compositors (unexposed) at one newspaper plant, significantly higher death rates were found among pressmen first employed at 40 years of age or more, and among men with 20 or more years of employment at this plant, than in compositors. There were no significant differences in death rates for men first employed at less than 40 years of age (including those working for more than 20 years). No obvious trends in causes of death were apparent.

3. Medicinal Mineral Oils

Skin and gastrointestinal toxicity, pulmonary toxicity and lung cancer and general carcinogenicity are discussed. No acute toxicity has been reported.

a. cutaneous toxicity

Skin sensitization with dinitrochlorobenzene (DNCB), followed by mineral oil applications and a DNCB challenge resulted in acanthosis, hypergranulosis and hyperkeratosis, mild inflammation of the corium and some cases of spongiosis and vesiculations. Mineral oil alone produced much less severe skin reactions, such as erythema, vesiculation and papules. The acanthotic activity of mineral oil was the basis for increased reactivity of the skin to DNCB.

Mineral oil acne and folliculitis occurred in a group of children, aged 2-10 years, after mineral oil was applied to the scalp following shampooing of the hair once a week for a few months. The skin reaction occurred mostly on the side of the face on which a particular child slept at night, due to contamination of the pillow cover with mineral oil. The condition cleared up about 6 months following elimination of the use of this oil.

b. gastrointestinal toxicity

Ingestion of mineral oil as a laxative causes lubrication of the rectal sigmoid and an abnormal fecal reservoir in the usually empty rectum. Mineral oil prevents absorption of fat soluble vitamins A, D, E and K, leading to vitamin deficiencies and their sequellae. The oil also coats particles of food in the intestine, interfering with absorption, and sometimes contributing to severe weight loss. Anal itching, involuntary discharge of oil and flatulence are some side effects of mineral oil ingestion. Due to the unphysiologic nature of the laxative effect, larger and larger quantities are needed as bowel function progressively worsens under the influence of mineral oil.

c. pulmonary toxicity

Aspiration of mineral oil into the lungs of persons using oily nose drops or mineral oil laxative occurs frequently, but evidence of oil pneumonia is usually only an incidental autopsy finding. The condition remains asymptomatic in most cases. The blandness of this oil allows it to enter the respiratory tract without triggering gag or cough reflexes.

Paraffinomas (circumscribed lesions containing oil surrounded by fibrotic tissue) or diffuse pneumonitis (oil droplets scattered throughout one or more lobes of the lung) may be observed. The pulmonary tissue response to oil is a foreign body reaction around alveoli, with diffuse infiltration of monocytes, eosinophils, plasma cells and giant cells. Fibrosis and formation of nodules around collections of oil occurs. Bronchial and bronchiolar inflammation, distortion and plugging with oil have been noted.

Oil pneumonia may be clinically present, but symptoms are non-specific, including dyspnea, cough, wheezing and chest pain. An X-ray picture of unresolved pneumonitis, hilar clouding, widespread fibrosis or a localized density may be found, and this picture is usually out of proportion to signs and symptoms of oil pneumonia.

Physiologic impairment may include decreased vital capacity, increased airway resistance, air trapping, and increased residual volume, which are suggestive of pulmonary emphysema. These findings are probably the result of fibrosis and broncho-inflammatory reactions to aspirated mineral oil.

d. carcinogenicity

Mineral oil aspiration pneumonia may coexist with lung cancer, but the relationship between the two entities is probably not causal. One case involved a 73-year-old woman with chronic mineral oil pneumonia. At autopsy, several adenocarcinomas were found in one extensively fibrotic lung section. Malignancies arising in areas of pulmonary fibrosis are probably a secondary phenomenon; according to one authority, there is no reason to suppose that carcinoma is more likely to develop in a scar induced by mineral oil than in a scar of any other origin. The rarity of reported cases argues against the carcinogenicity of mineral oil in the lungs of humans.

No excess of malignancies has ever been reported in humans receiving injections or instillations containing mineral oil.

D. Animal Toxicity

The effects of SGF No. 1 and No. 2 and their representative models are presented separately. Tables 10 to 14, at the end of this chapter, summarizes the animal studies reported.

1. SGF No. 1

In a study done in 1945, Lushbaugh exposed various animals to oil mists of SGF No. 1 fog oil, in concentrations of 63 mg/m^3, for thirty minutes of every hour of every day for approximately one year. The results follow.

a. pulmonary toxicity and cancer

Pulmonary changes in 125 1-month-old strain A mice included oil collections in peribronchial and mediastinal lymph nodes, but no evidence of lipoid pneumonia. In 4 rabbits, oil was found in microscopic amounts in macrophages in the mediastinal lymph nodes and lymphatic channels of the lungs and pleura, with some oil containing macrophages intra-alveolarly and subpleurally. No increase in pneumonias was noted between exposed and unexposed rabbits. In 80 albino rats, oil accumulation in the lungs was minimal, being similar to the deposits in rabbits, and there was no increase in pneumonias over control rats. Pulmonary oil accumulation in 7 Macaca mulatta monkeys was described as focal pneumonia with interstitial inflammation. Oil containing macrophages were thinly scattered throughout alveoli, advancing toward pulmonary lymphatics as oil exposure continued. Macrophages had both fine and large

oil droplets. Longer exposures lead to increased numbers of fibroblasts and connective tissue in the lipophage-containing areas, and the formation of condensed fibrotic nodules containing oil. The incidence of infectious pneumonia in exposed monkeys was greatly increased over unexposed controls.

In the month-old strain A mice, which are highly susceptible to carcinogenic influences, oil inhalation failed to influence either the incidence or time of occurrence of pulmonary neoplasms. Tumors in exposed mice also bore no spatial relationship to inhaled oil deposits. None of the exposed rabbits, rats or monkeys developed pulmonary tumors.

b. gastrointestinal toxicity and cancer

There was marked wasting, due to decreased food intake, in all oil-exposed monkeys after 30 days. The stomachs of killed monkeys were shrunken and fibrotic. The gastric mucosa was thickened and ulcerated, and all but the mucus-secreting cells of the gastric mucosa were atrophic. Infiltration of gastric mucosal cells into the submucosal connective tissue, possibly gastric adenocarcinoma, was observed in two monkeys exposed for 97 and 100 consecutive days, respectively. The etiology of gastric changes was probably the swallowing of oil filtered out of nasal passages, oil ingested with food, and general oil contamination of the bodies of the monkeys.

c. other effects

After one month of oil exposure, the monkeys had thinning of the fur. Bald areas were observed over more than half of the body of monkeys by 100 days of exposure. No other observations were reported for any of the animals in this experimental SGF No. 1 fog oil mist exposure.

2. SGF No. 1 Models

a. lethal doses

Diesel fuel was found to have an oral LD_{50} of 16.0 ml/kg of body weight for 138 Wistar rats weighing 180-340 g which were administered the fuel by stomach tube.

The subacute lethal dose of diesel fuel in rats was calculated to be 6.9 ml/kg of body weight per day administered by stomach tube.

An intratracheal administration of LD_{50} for 175-300 g Wistar rats was 0.05 ml of diesel fuel per rat.

Aspiration of 0.02 ml of diesel fuel by 2 male albino Wistar rats weighing 300-400 g caused the death of both animals in 24 hours.

b. pulmonary toxicity

Diesel fuel aerosols, up to 10,000 mg/m^3, did not damage the pulmonary surfactant layer of 175-300-g Wistar rats exposed for unspecified lengths of time.

An ewe which ingested diesel fuel soaked grass developed dyspnea and respiratory difficulties of unspecified nature.

Kerosene aerosols, up to 10,000 mg/m^3, did not damage the pulmonary surfactant layer of 175-300-g Wistar rats exposed for unspecified lengths of time.

In six mice exposed to 6900 mg/m^3 of deodorized kerosene aerosol, there was no respiratory tract irritation, but slight respiratory depression.

Wistar rats (175-300 g) given 2.0-3.0 ml of kerosene by direct instillation into the duodenum, developed no changes in pulmonary surfactant, as measured by lung deflation under low transpulmonary pressures.

Wistar rats weighing 175-300 g were given 0.01-0.10 ml of diesel fuel by tracheal instillation, and surfactant layer damage was noted after 15 minutes, returning to normal after 48 hours in animals remaining alive.

In Wistar rats (175-300 g) given 0.1 ml/kg of diesel fuel by tracheal instillation, a chemical pneumonitis developed into pneumonitis. After 14 days, there were still microscopic patches of resolving pneumonia in some rats. Kerosene effects were indistinguishable within this experimental setup.

Two albino Wistar rats (350 g) died within 24 hours after aspiration of 0.02 ml of diesel fuel. Pulmonary findings included severe edema, hemorrhage, liver-like appearance, tachypnea, dyspnea, cyanosis, and a blood-tinged frothy nasal discharge.

Rats aspirating 0.2 ml of kerosene also developed acute chemical pneumonitis.

c. neurotoxicity

Loss of coordination and sluggishness were noted in albino rats (90-120 g) after 6 hours of exposure to 9600 mg/m^3 of deodorized kerosene aerosols.

d. effects on body weight

No adverse effects on body weight were noted after 6 male albino rats (90-120 g) were exposed to 9600 mg/m^3 of deodorized kerosene aerosols for 6 hours a day on 4 consecutive days, and observed for 14 additional days. A 13-week inhalation of 100 mg/m^3 deodorized kerosene aerosols (6 hours per day, 5 days per week) had no adverse effect on weight in these male rats.

Four cats exposed to deodorized kerosene aerosol concentrations of 6400 mg/m^3 for 6 hours, and observed for 14 days, had no alterations in weight gain. A borderline but significant weight increase was noted in beagles after 13 weeks of exposure to 20 mg/m^3 of deodorized kerosene aerosols.

e. effects on behavior

Loss of coordination and sluggishness occurred in albino rats (90-120 g) after 6 hours of exposure to 9600 mg/m^3 of kerosene aerosols.

A stiff uncertain gait and reduced appetite were noted in a cow which ingested up to 7 liters of diesel fuel.

f. hematotoxicity

Diesel fuel ingestion in 138 Wistar rats, 180-340 g, in a dose of 20-25 ml/kg of body weight per day caused a significant drop in hemoglobin after 14 days, significant reticulocytosis after 7 and 14 days, neutrophilic granulocytosis, lymphocytopenia, and thrombocytopenia after 7 days.

A slight elevation in number of neutrophils was noted in beagles exposed to 100 mg/m^3 of deodorized kerosene aerosols for 13 weeks (6 hours a day, 5 days a week).

In an ewe which ingested diesel fuel soaked grass, hematologic changes included neutrophilic leukocytosis and a moderate normochromic anemia.

Male Wistar rats (250 g) received applications of undiluted diesel fuel to the skin of their tails for 6 hours each day for 10 days. Hemoglobin was decreased after around 2 weeks, reticulocytosis was noted from 2-4 weeks, leukocytosis was noted between the second and third weeks, and neutrophilic granulocytosis was present up to three weeks. No thrombocytic or lymphocytic changes were noted.

g. effects on serum enzymes

In male Wistar rats (250 g) administered diesel fuel by tail painting for 6 hours a day for 10 consecutive days, increases in aspartate aminotransferase and intermediate lactate dehydrogenase (LDH) isoenzyme activities, and decreases in LDH heart and liver (muscle) enzyme activities were noted.

In 138 rats (250 g) ingesting 20-25 ml/kg of body weight per day of diesel fuel, there were elevations in malate dehydrogenase, aspartate aminotransferase and alanine aminotransferase activities, in comparison with unexposed controls.

h. effects on blood sugar

Ten rabbits fed 2.5 ml of fuel oil demonstrated a gradual drop in blood sugar to 23% below normal between 5 and 7 hours after dosing, with a return to control levels by 12 hours.

i. immunotoxicity

In rabbits intermittantly exposed to diesel fuel fumes for 2 hours a day

for 80 days, antibody production to typhoid-paratyphoid vaccine given on day 0 and day 50 was reduced when compared with unexposed controls. There was a steady increase in immune titers, indicating an absence of the secondary immune response in exposed rabbits.

j. gastrointestinal toxicity

An ewe which ingested diesel fuel soaked grass developed weight loss and increased rumenal peristalsis. The rumenal wall was found to contain raised ulcerating caseonodular lesions up to 3 cm. in diameter.

k. dermatotoxicity

Negative results were reported following skin sensitization of 24 white male guinea pigs with diesel fuel.

Diesel fuel was classified as a mild primary skin irritant in 10 white 3500-g Belgian rabbits.

Epidermal splitting, exfoliation, hair loss and a papular rash resulted after painting the tail skin of Wistar rats for 6 hours a day for 10 consecutive days with undiluted diesel fuel. The effect receded 2-3 weeks after termination of exposure.

Erythema, desquamation, induration, hair loss and rhagades occurred in the skin of 5 albino guinea pigs after application of diesel fuel to the dorsal skin once a day for 5 days. Crusting and ulceration were noted by the 12th day. Healing occurred within 10 days of termination of treatment, and hair regrowth began after 15 days.

Diesel fuel promoted granulation tissue formation in Wistar rats which had dermal implants containing diesel fuel placed in the dorsal skin for 10 days. The effect was dose dependent.

l. carcinogenicity

Skin tumors occurred in 18/100 mice painted daily with a heavy grade of diesel fuel in the interscapular region. In mice painted twice a week, 1/100 developed a tumor. Lighter grade diesel fuel produced only dermatitis in similar mouse experiments. No other evidence of carcinogenicity of SGF No. 1 models is reported in the literature.

m. other effects

There are no reports on effects on reproduction, growth, teratogenicity, fetotoxicity, or other organs or systems than those mentioned above.

3. SGF No. 2 Models

No investigations of animal toxicology of SGF No. 2 fog oil are reported in the literature. Acute and chronic toxicity of petroleum lubricating oils

and white oils derived from refining them by removal of their aromatic compounds are presented.

a. lethal doses

Liquid petrolatum aerosol, in concentrations of 4500 mg/m^3 in a 2-hour exposure, was lethal for 2/6 albino mice weighing 25-35 g, within two days following exposure.

In male albino Wistar rats weighing 200-300 g, aspiration of 0.2 ml of automotive lubricating oil caused the death of 1/5 in 24 hours.

Mice fed 0.5 ml of white mineral oil per mouse per day mixed with the diet (20 ml/kg of body weight) died after 7-10 days.

Rats fed 1.0 ml of white mineral oil per rat per day (5 ml/kg of body weight) died after 7-10 days.

b. pulmonary toxicity

Lubricating oil and white mineral oil aerosols, inhaled by six 25-35 gram albino mice, in concentrations of 4330-4500 mg/m^3, for 2 hours, produced the following pulmonary changes: oil retention in terminal bronchioles and alveolar ducts; vigorous and immediate oil phagocytosis which was complete in 48 hours; no inflammatory response; and no deaths. Albino mice exposed to these oil aerosols for about 90 hours developed marked oil retention in all divisions of the respiratory tree. Coalescence of oil into giant droplets was noted, with the majority of the oil being intracellular, and occasional areas of oil pneumonia. Twenty percent of these animals died from acute lipoid pneumonitis.

Albino mice weighing 20-25 grams were exposed to 200 mg/m^3 of lubricating or mineral oil aerosols for 4 hours. Hyperplasia of the tracheobronchial epithelium was found in mice sacrificed from 18-144 hours following the exposure. Alveolar macrophages increased in number up to 96 hours following exposure, but the response was "very mild". No oil pneumonias were observed. Mice exposed for 7 hours a day for 4 days to these oils (200 mg/m^3) developed no pulmonary lesions within 96 hours of the last exposure.

Male Wistar rats (200 g) exposed to mineral aerosols, 30,000 mg/m^3, for 6 hours a day for up to 3 weeks developed focal oil granulomas characteristic of a foreign body type of response to the oil in the lungs, as well as classic lipoid pneumonia.

Aspiration of 0.2 ml of automotive lubricating oil in albino Wistar rats (200-300 g) resulted, after 24 hours, in a low-grade localized oil pneumonia with slight inflammatory response.

Exposure of white mice to lubricating oil aerosols, 132 mg/m^3, 30 minutes per hour, 24 hours a day for 100 consecutive days, resulted in accumulations

of oil in macrophages in lungs and tracheobronchial lymph nodes. An average of 1.65 mg of oil accumulated in one mouse lung, representing 0.4% of total wet lung weight. A hundredth of the total amount of inhaled oil was retained in the lungs. In rats exposed to 100 mg/m^3 of mineral oil aerosols for 6 hours a day, 5 days a week, for up to 26 months, progressive oil macrophage accumulations were also noted, along with interstitial pneumonitis. Pneumonitis resulted after exposure of rats to lubricating oils in concentrations up to 60 mg/m^3, 5 hours a day for up to 6 months. Leukocytic infiltrates, connective tissue proliferation, and peribronchial and perivascular lymphocytic infiltrates were described.

Male Golden Syrian hamsters and male Dutch rabbits exposed to 100 mg/m^3 of mineral oil aerosols for 5 days a week, 6 hours a day for 15 months, exhibited no major lung tissue response. In male mongrel dogs, however, diffuse macrophage accumulations and oil granulomas within or near alveoli, small bronchi and hilar lymph nodes were noted after 26 months of oil aerosol exposure.

Seven rhesus monkeys exposed to 132 mg/m^3 of lubricating oil aerosols, for 30 minutes per hour, 24 hours per day for up to 100 consecutive days showed moderate degrees of subacute and chronic hyperplastic panbronchiolitis, granulomas, and diffuse bronchopneumonia. Large amounts of oil did not accumulate in the lungs.

c. hepatotoxicity

In mice and rats fed mineral oil, 20 ml/kg and 5 ml/kg of body weight, respectively, diffuse fatty degeneration of the hepatic parenchyma occurred. Intense liver congestion was found in monkeys fed up to 2.2 ml/kg of body weight of mineral oil.

White male rats exposed to up to 50 mg/m^3 of lubricating oil aerosols for 6 months developed liver degeneration.

Skin painting of mice with mineral oil for up to 90 weeks caused round cell periportal infiltration, xanthomata of endothelial cells scattered throughout the liver, degeneration and fatty infiltration. The animals had ingested the oil by licking the treated skin areas.

No liver changes due to the exposure of mice, rats, hamsters or rabbits to mineral oil aerosols, 100 mg/m^3, for 6 hours a day, 5 days a week for up to 26 months, were reported.

d. nephrotoxicity

Degenerative changes in ascending tubules of the kidneys of mice were observed after feeding them 20 ml/kg of body weight of white mineral oil in the diet. Kidney congestion occurred after feeding one monkey 2.25 ml/kg of white mineral oil per day (total 195 ml) for 3 months.

No nephrotoxicity was reported after exposure of mice, rats, hamsters, rabbits or dogs to 132 mg/m^3 lubricating oil aerosols for 30 minutes of every hour for 100 consecutive days.

e. gastrointestinal toxicity

Small ulcers and chronic inflammation of the large intestine were observed in a 2.7 kg monkey fed a total of 96 ml of white mineral oil in doses of 2.2 ml/kg of body weight per day.

The stomach fundus and duodenum of mice, rats, hamsters, rabbits and dogs showed no pathological changes due to exposure of these animals to 100 mg/m^3 of mineral oil aerosols for 6 hours a day, 5 days a week for up to 26 months.

f. cardiovascular toxicity

White mineral oil fed in the diet to three monkeys, in total doses of 96 ml, 36 ml and 195 ml caused increased vascularity and congestion in most internal organs. The authors felt that the oil's chief action was on the blood vessels supplying these organs.

Myocardial degenerative changes occurred in rats exposed to lubricating aerosols, 60 mg/m^3, 5 hr/day for 6 months. However, no histologic changes were reported in the heart of mice, rats, hamsters, rabbits or dogs after exposures to 100 mg/m^3 of mineral oil aerosols for 6 hours a day, 5 days a week for up to 26 months.

g. hematotoxicity

Elevated polymorphonuclear leukocyte counts were reported after exposure of mice to mineral oil fumes.

Decreased leukocyte phagocytic activity occurred in rats exposed for 6 months to aerosols of lubricating oils in concentrations up to 60 mg/m^3. Leukocytosis and lymphocytopenia of peripheral blood was noted.

Rabbits and dogs exposed to 100 mg/m^3 of mineral oil aerosols for 26 months (6 hours a day, 5 days a week) showed no abnormalities in hematocrit, hemoglobin or white blood cell counts after quarterly evaluations.

h. neurotoxicity

A higher neuromuscular excitability threshold, increased parasympathetic tone, and central nervous system depression, manifested by decreased respiratory rate, slower heart rate, lower voltage of EKG peaks, and decreased arterial blood pressure were reported after 6 months of exposure of rats to lubricating oil aerosol concentrations of up to 60 mg/m^3 for 5 hours per day.

i. immunotoxicity

Lubricating oil aerosols, in concentrations up to 60 mg/m^3, produced increased blood neuraminic acid levels, lowered albumin, increased alpha 1, alpha 2 and beta globulins, lower serum agglutinin titers and decreased

leukocyte phagocytic activity in rats exposed for 6 months. These changes were indicative of depressed immune reactivity.

Guinea pigs and rats exposed to 10 mg/m^3 of lubricating oil aerosols for 4 hours a day for 5 months had lowered antibody titers to typhoid and paratyphoid vaccine and reduced phagocytic activity of the blood of non-vaccinated animals to non-virulent *Staphylococcus aureus*.

Proliferation of reticulo-endothelial cells of the splenic pulp occurred in mice fed 20 ml/kg of body weight per day of white mineral oil for up to 10 days.

j. dermatotoxicity

Mice fed 20 ml/kg of body weight per day of white mineral oil for up to 10 days developed rough dry skin, erect hairs, and epidermal hyperkeratosis.

Monkeys exposed to automotive lubricating oil aerosols, in concentrations of 132 mg/m^3, for 30 minutes of every hour of every day for up to 100 days developed oily fur, leading to thinning and bald areas over the abdomen, head and back. The fur returned to normal after discontinuation of oil exposure.

Hyperkeratosis occurred in Holstein-Friesian calves which were administered white lubricating oil to the skin for 8 weeks, as well as in guinea pigs treated every other day for 4 days with mineral oil or lubricating oil. Lubricating oils were acanthogenic in guinea pig skin.

Liquid petrolatum increased the cutaneous reactivity of the skin of albino guinea pigs previously sensitized to 2,4-dinitrochlorobenzene. Erythema, scaling and hyperkeratosis, acanthosis and hypergranulosis were described.

k. carcinogenicity

In the CAF_1/Jax mouse, which has a genetically based, spontaneous pulmonary tumor susceptibility, exposures 5 days a week, 6 hours a day for 16 months to 100 mg/m^3 of mineral oil caused an altered rate of tumor formation over unexposed control mice. The number of tumors in oil exposed mice after 12 and 13 months was less than expected, if oil mist was to be considered an accelerator. Mild tumor acceleration occurred only after 10 and 11 months of exposure.

Inhalation of mineral oil aerosols by 40 guinea pigs produced 8 alveolar epithelializations, 1 neoplasm and 17 other pulmonary lesions. Exposures to oil smoke in 40 guinea pigs lead to 4 alveolar epithelializations, 1 neoplasm and 9 other pulmonary lesions. No tumors occurred in unexposed animals.

Mineral oil was classified as a non-accelerator of skin cancer in mice, in doses of 50 mg applied 3 times a week to the dorsal epithelium. Lubricating oil fractions containing polycyclic aromatic hydrocarbons were weakly carcinogenic in mouse skin.

A solvent refined mineral oil was non-carcinogenic in mouse skin, while sulfuric acid treated lubricating oil produced 9 skin cancers in 15 mice.

Benzo(a)pyrene-containing lubricating oil accelerated the rate of tumor induction by 7,12-dimethylbenz(a)anthracene in mice given 14 applications of 0.25 ml of oil over 9 1/2 weeks. Of 24 animals, 11 developed malignancies. There were 9 squamous cell carcinomas, 1 basal cell carcinoma and 1 sarcoma. In 24 animals treated with this oil alone, 6 animals developed skin tumors in 84 weeks, of which there were 1 sarcoma, 2 carcinosarcomas, 3 squamous cell carcinomas and 2 benign squamous papillomas.

Paraffin oil painted on the nape of the neck of mice twice weekly for 24 months was mildly carcinogenic. Of 50 mice, there were 1 squamous cell carcinoma, 1 papilloma and 20 leukemias or lymphomas.

l. mutagenicity

Arene oxides of benzo(a)pyrene are mutagenic in strains of *Salmonella typhimurium* and in Chinese hamster V79 cells, but the value of mutation experiments in determining the carcinogenicity of arene oxides - intermediary metabolites of aromatic hydrocarbons present in lubricating oils - was considered to be uncertain.

m. other effects

Teratogenicity, fetotoxicity, effects on growth or other organs or systems not previously discussed have not been reported in the literature.

E. Pharmacokinetics

SGF No. 1 and SGF No. 2 and their models will be discussed individually.

1. SGF No. 1 and Model Fuels

There is no data on the absorption, distribution, metabolic biotransformation or excretion of SGF No. 1, and research on model fuels is brief.

Diesel fuel is absorbed slowly through the skin of rats. Absorption in the gastrointestinal tract of paraffins present in SGF No. 1 involves oxidation to corresponding acids, and uptake into the lymphatics, in rats, guinea pigs, goats and possibly humans. Distribution of the oxidized fatty acids into liver and fatty tissue has been demonstrated in studies with labelled hexadecane and octadecane. Diesel fuel is excreted slowly by rats fed large doses. It has been detected in the urine of a child who drank the substance. Kerosene caused a marked increase in urinary glucuronic acid excretion and a moderate increase in urinary inorganic sulfates in rabbits two days after oral administration of kerosene. The conversion of polycyclic aromatic hydrocarbons to oxides of phenanthrene and benzanthracene, followed by mercapturic acid formation is reported.

2. SGF No. 2 and Lubricating Oils

Oil aerosol droplets which are inspired are absorbed by the lung and phagocytized by macrophages. Medicinal mineral oil absorption through the gastrointestinal tract of humans accounts for about 2% of laxative doses. Absorbed oil is found in spleen, liver, and mesenteric lymph nodes. In cases of lipoid pneumonia, the oil is found in hilar and portal lymph nodes, liver and spleen.

The metabolism of the branched and cyclic alkanes in mineral oils has not been documented. The polycyclic aromatic hydrocarbons present in lubricating oils may be metabolized in the liver to the epoxides, which are subsequently converted to phenols and trans-hydrodiols; these may be conjugated with glutathione and metabolized to mercapturic acids for urinary excretion.

Polycyclic aromatic hydrocarbons are enzymatically converted to K-region epoxides in microsomes of various tissues. These epoxides are more active carcinogens than the parent compounds in some cases, as well as having mutagenic properties. The enzyme, aryl hydrocarbon hydroxylase, which is responsible for this conversion, is a genetically controlled, inducible enzyme, found in human skin and lung tissue as well as a number of other sites.

Most ingested mineral oil is excreted unchanged in the feces. Inhaled oil may be expectorated, removed from the lungs by lymphatics, or encysted in granulomas. Large deposits of oil accumulate in the lungs. In rats, the kidneys were only able to excrete trace quantities of mineral oil, although the oil was demonstrated in kidney homogenates following dosing.

TABLE 10

Animal Toxicity of SGF No. 1 Aerosol

Animal	Experimental Data	Results	Reference
250 1-month old strain A mice mice	63 mg/m^3 aerosol of SGF No. 1; cycles of 30 min of aerosol and 30 min of room air for 343 days	excess of pulmonary tumors; oil deposition in mediastinal and peribronchial lymph nodes; no excess pneumonia	Lushbaugh et al., 1950 (89)
4 rabbits	same as above for one year	no pulmonary tumors; oil deposition in pulmonary lymphatics	Lushbaugh et al., 1950 (89)
80 albino rats	same as above for one year	no pulmonary tumors; no excess pneumonia; minimal oil accumulation in lungs	Lushbaugh et al., 1950 (89)
7 rhesus monkeys	same as above for 100 days	5 deaths - after 44, 67, 71, 77 and 97 days of exposure; progressive thinning of fur and baldness; progressive pulmonary oil accumulation and focal pneumonia; excess infectious pneumonia; gastric ulcerations and atrophy; 2 gastric adenocarcinomas	Lushbaugh et al., 1950 (89) and Lushbaugh et al., 1945 (90)

TABLE 11

Animal Toxicity of SGF No. 1 Models

A. Aerosol Exposure

Animal	Experimental Data	Results	Reference
Wistar rats	10,000 mg/m^3 vapors of diesel fuel or kerosene; unspecified duration of exposure	no damage to pulmonary surfactant layer	Keen, 1968 (14)
6 albino rats	9600 mg/m^3 aerosol of deodorized kerosene; 6 hr/day for 4 consecutive days	loss of coordination; sluggishness; dermatitis; normal weight gain	Carpenter et al., 1976 (7)
25 rats	50-100 mg/m^3 aerosol of deodorized kerosene; 6 hr/day, 5 days/wk for 13 weeks	2 died after 16 and 30 days; bronchopneumonia; elevated urine pH; erythrocytopenia; no progressive adverse effects	Carpenter et al., 1976 (7)
rats	14,400 mg/m^3 vapors of C_9-C_{10} aromatic distillate for 7 hours	acute LC_{50}	Nau et al., 1966 (41)
rats	3200-5200 mg/m^3 vapors of C_9-C_{10} aromatic distillate; 18 hr/day; up to 2,424 hours of exposure	decreased rate of weight gain; neutrophilia; lymphocytopenia, decreased total leukocyte count; bilateral cataracts; hemorrhagic lungs, liver, kidneys, spleen; increased myelocytic precursors in bone marrow	Nau et al., 1966 (41)
rats	260-1000 mg/m^3 vapors of C_9-C_{10} aromatic distillate; 8 hr/day; 5 days/wk; 700 hr. total	no adverse affects	Nau et al., 1966 (41)
rats	4600 mg/m^3 vapors of C_{11}-C_{12} aromatic distillate for 7 hours	acute LC_{50}	Nau et al., 1966 (41)

TABLE 11 (Cont.)

Animal Toxicity of SGF No. 1 Models

A. Aerosol Exposure

Animal	Experimental Data	Results	Reference
37 rats	3200 mg/m^3 vapors of C_{11}-C_{12} aromatic distillate; 18 hr/day; up to 1683 hr. of exposure	50% died after 18 hr; decreased rate of weight gain; hemorrhagic lungs; liver; splenic dystrophy; decreased total leukocyte count; neutrophilia; lymphocytopenia; watery bone marrow; dermatitis	Nau et al., 1966 (41)
rabbits	diesel fuel and motor oil fumes (100:6 mixture); 2 hr/day for 80 days	reduced antibody production to typhoid-paratyphoid vaccine; absence of secondary response	Samal et al., 1975 (91)
mice	6900 mg/m^3 deodorized kerosene aerosol (duration not specified)	slight depression of breathing rate; no respiratory tract irritation	Carpenter et al., 1976 (7)
CFW mice	9700 mg/m^3 vapors of C_9-C_{10} aromatic distillate; 3.75 hr. exposure	Acute LC_{50}	Nau et al., 1966 (41)
CFW mice	3400 mg/m^3 vapors of C_{11}-C_{12} aromatic distillate; 3.7 5 hr. exposure	Acute LC_{50}	Nau et al., 1966 (41)
3 rhesus monkeys	1000 mg/m^3 vapors of C_9-C_{10} aromatic distillate; 7 hr/day; 5 days/wk; 90 exposures	hair loss; dry skin; sedation; tremor; leukocytopenia; neutrophilia; lymphocytopenia; decreased erythrocytic and myelocytic precursors in bone marrow	Nau et al., 1966 (41)
3 rhesus monkeys	260 mg/m^3 vapors of C_9-C_{10} aromatic distillate; 7 hr/day; 5 days/wk; 90 exposures	elevated hematocrit; leukocytopenia; neutrophilia; lymphocytopenia	Nau et al., 1966 (41)

TABLE 11 (Cont.)

Animal Toxicity of SGF No. 1 Models

A. Aerosol Exposure

Animal	Experimental Data	Results	Reference
4 rhesus monkeys	300 or 1280 mg/m^3 vapors of C_{11}-C_{12} aromatic distillate; 7 hr/day; 5 days/wk; 90 exposures	eye and skin irritation; diarrhea; neutrophilia and lymphocytopenia; increased erythrocytic and decreased myelocytic precursors in bone marrow	Nau et al., 1966 (41)
beagles	100 mg/m^3 deodorized kerosene aerosol; 6 hr/day; 5 days/wk for 13 weeks	no adverse effects	Carpenter et al., 1976 (7)
beagles	20 mg/m^3 given as above	mean weight increase	Carpenter et al., 1976 (7)
4 cats	6400 mg/m^3 deodorized kerosene aerosol; 6 hours	no adverse effects in 14 days	Carpenter et al., 1976 (7)

B. Intratracheal Aspiration

Wistar rats	0.01-0.10 ml/animal of diesel fuel by intratracheal route	pulmonary surfactant layer damage	Keen, 1968 (14)
2 Wistar rats	0.02 ml/animal of diesel fuel by mouth during apneic state	both rats died in 24 hr of acute aspiration pneumonitis and pulmonary edema	Gerarde, 1963 (93)
Wistar rats	0.10 ml/kg (~ 0.025 ml/animal) of body weight of diesel fuel or kerosene by intratracheal route	pneumonia; resolution in 14 days	Keen, 1968 (14)
Wistar rats	0.05 ml/animal of diesel fuel by intratracheal route	acute LD_{50}	Keen, 1968 (14)

TABLE 11 (Cont.)

Animal Toxicity of SGF No. 1 Models

B. Intratracheal Aspiration

Animal	Experimental Data	Results	Reference
rabbits	1.0 ml/animal of diesel fuel by introtracheal route	progressive interstitial pneumonitis; alveolar hemorrhage; bronchiolar necrosis after 6-8 days	Haraszti and Sovari, 1968 (48)

C. Skin Application

Wistar rats	undiluted diesel fuel applied to tail skin 6 hr/day for 10 days	dermatitis; hair loss; decreased hemoglobin; erythrocytopenia; reticulocytosis; leukocytosis; neutrophilia; lymphocytopenia	Starek et al., 1976 (97)
5 albino guinea pigs	diesel fuel applied to intracapular skin 5 times/wk for 19 days	erythema; desquamation; hair loss; ulceration and crusting	Bien and Buntrock, 1969 (99)
albino guinea pigs	various petroleum fuel distillates applied to skin every other day; 4 applications total	hyperplasia; hyperkeratoses; hair loss; aromatic fuels more toxic than paraffinic fuels	Hoekstra and Phillips, 1963 (85)
24 guinea pigs	Landsteiner and Jacobs skin sensitization method with diesel fuel	no skin sensitization	Starek et al., 1976 (97)
10 white Belgian rabbits	Draize method with diesel fuel	mild primary irritant to skin and conjunctiva	Starek et al., 1976 (97)
79 C_3H mice	0.10-0.15 g/animal of C_9-C_{12} aromatic distillate applied to skin 3 times/week; 150 applications total	dry, thick, scaly skin; hyperkeratosis; epidermal atrophy; dermatitis; ulceration	Nau et al., 1966 (41)
100 mice	intrascapular skin; daily application of light grade diesel fuels	dermatitis	Twort and Twort, 1935 (100)

TABLE 11 (Cont.)

Animal Toxicity of SGF No. 1 Models

C. Skin Application

Animal	Experimental Data	Results	Reference
100 mice	intrascapular skin; daily application of dirty-looking heavy grade diesel fuels	18 tumors; 3/18 became malignant	Twort and Twort, 1935 (100)

D. Oral Administration

Wistar rats	20-25 ml/kg of body weight/day diesel oil by gastric intubation for 14 days	hemoglobinemia; reticulocytosis; neutrophilia; lymphocytopenia; thrombocytopenia; elevated serum malate dehydrogenase, apartate and alanine aminotransferase	Starek et al., 1975 (92)
138 Wistar rats	16.0 ml/kg of bodyweight diesel oil by gastric intubation	acute oral LD_{50}	Starek et al., 1975 (92)
5 Wistar rats	6.9 ml/kg of bodyweight/day diesel oil by gastric intubation for approx. 3 weeks	subacute oral LD_{50}	Starek et al., 1975 (92)
9 Wistar rats	2.0-3.0 ml/animal of kerosene by duodenal instillation	no changes in lung stability in 18-24 hr.	Keen, 1968 (14)
10 rabbits	1.0 ml/kg of bodyweight of fuel oil orally	23% drop in blood sugar in 5-7 hr; return to normal levels by 12 hr.	Tani, 1939 (94)
cow	approx. 7 liters of diesel fuel ingested accidentally	low grade fever; diarrhea; constipation; lowered milk production; stiff uncertain gait; swelling of hind fetlocks; recovery in 8 days	Messerli, 1969 (95)

TABLE 11 (Cont.)

Animal Toxicity of SGF No. 1 Models

D. Oral Administration

Animal	Experimental Data	Results	Reference
ewe	ingestion of diesel fuel-soaked grass	weakness; weight loss; diesel fuel odor on breath, urine and feces; slight pulmonary involvement; nodular lesions on inner rumen wall; complete loss of fleece; neutrophilia; normochromic anemia	Ranger, 1976 (96)

TABLE 12

Animal Toxicity of SGF No. 2 Models

A. Acute Aerosol Exposure

Animal	Experimental Data	Results	Reference
30 albino mice	approx. 200 mg/m^3 aerosols of either S.A.E. 10-20 motor oil or mineral oil; 4 hr exposure	very mild hyperplasia of tracheobronchial epithelium	Wagner et al., 1961 (27)
6 albino mice	4330 mg/m^3 aerosol of S.A.E. 10 motor oil; 2 hr exposure	oil retention in terminal bronchioles and alveolar ducts; vigorous oil phagocytosis	Shoshkes et al., 1950 (69)
7 albino mice	4330 mg/m^3 aerosol of S.A.E. 10 motor oil; 92 hr exposure total (intermittent schedule)	one death; heavy oil retention in all divisions of respiratory tree; pneumonia; coalescence of oil into giant droplets (≥ 30 μ diameter)	Shoshkes et al., 1950 (69)
6 albino mice	4500 mg/m^3 aerosol of S.A.E. 10 motor oil; 2 hr exposure	2 deaths; oil retention in terminal bronchioles and alveolar ducts; vigorous oil phagocytosis	Shoshkes et al., 1950 (69)
13 albino mice	4500 mg/m^3 aerosol of S.A.E. 10 motor oil; 90 hr exposure total (intermittent schedule)	3 deaths; extremely heavy oil retention in all divisions of respiratory tree; pneumonia; coalescence of oil into giant droplets (≥ 30 μ diameter)	Shoshkes et al., 1950 (69)
20 Wistar rats	30,000 mg/m^3 aerosol of mineral oil 6 hr/day for 3 wk.	increased macrophages and foam cells in alveolar lumina and septae; oil deposition in 2 weeks; decreased adenosine triphosphate activity of macrophages; focal oil granulomas and pneumonia in 3 weeks	Eckert and Kandt, 1975 (101)

TABLE 12 (Cont.)

Animal Toxicity of SGF No. 2 Models

B. Chronic Aerosol Exposure

Animal	Experimental Data	Results	Reference
6 rhesus monkeys	132 mg/m^3 aerosol of S.A.E. 10 motor oil; 100 days; schedule of 30 min aerosol alternating with 30 min room air	2 deaths; oil accumulation in lungs followed by gradual clearing over one year; pneumonia; bronchiolitis; pulmonary fibrosis; pulmonary edema; weight loss; atrophic stomach; fur loss	Lushbaugh et al., 1945 (90) and Wagner et al., 1964 (105)
80 white mice	132 mg/m^3 aerosol of S.A.E. 10 motor oil; 100 days; schedule of 30 min. aerosol alternating with 30 min room air	gradual oil accumulation in lung macrophages in peripheral and subpleural alveoli; no free oil; oil macrophages in tracheobronchial lymph nodes; minimal toxicity	Lushbaugh and Cannon, 1942 (104)
120 CF No. 1 mice	5 or 100 mg/m^3 aerosol of lubricating oil; 6 hr/day; 5 days/wk; 12 months	lung oil macrophages scattered randomly; no major lung response; no other adverse effects	Wagner et al., 1964 (105)
160 Holtsman-Sprague-Dawley rats	5 or 100 mg/m^3 aerosol of lubricating oil; 6 hr/day; 5 days/wk; 26 months	pulmonary tissue damage indicated by elevated lung alkaline phosphatases; progressive interstitial pneumonia only with higher concentration	Wagner et al., 1964 (105)
albino rats	10-125 mg/m^3 aerosol of spindle oil; 4 hr/day for 5 months	lowering of antibody titers to typhoid and paratyphoid vaccine; reduced phagocytic activity in blood of non-vaccinated rats	Bruskin, 1965 1965 (106)
30 rats	13, 30 or 60 mg/m^3 aerosols of industrial lubricating oils (without additives); 5 hr/day for 6 months	serum neuraminic acid levels increased progressively; decrease of serum albumin and leukocyte phogocytic activity; increased serum globulins	Lutov, 1973 (107)

TABLE 12 (Cont.)

Animal Toxicity of SGF No. 2 Models

B. Chronic Aerosol Exposure

Animal	Experimental Data	Results	Reference
6 rhesus monkeys	132 mg/m^3 aerosol of S.A.E. 10 motor oil; 100 days; schedule of 30 min aerosol alternating with 30 min room air	2 deaths; oil accumulation in lungs followed by gradual clearing over one year; pneumonia; bronchiolitis; pulmonary fibrosis; pulmonary edema; weight loss; atrophic stomach; fur loss	Lushbaugh et al., 1945 (90) and Wagner et al., 1964 (105)
80 white mice	132 mg/m^3 aerosol of S.A.E. 10 motor oil; 100 days; schedule of 30 min. aerosol alternating with 30 min room air	gradual oil accumulation in lung macrophages in peripheral and subpleural alveoli; no free oil; oil macrophages in tracheobronchial lymph nodes; minimal toxicity	Lushbaugh and Cannon, 1942 (104)
120 CF No. 1 mice	5 or 100 mg/m^3 aerosol of lubricating oil; 6 hr/day; 5 days/wk; 12 months	lung oil macrophages scattered randomly; no major lung response; no other adverse effects	Wagner et al., 1964 (105)
160 Holtsman-Sprague-Dawley rats	5 or 100 mg/m^3 aerosol of lubricating oil; 6 hr/day; 5 days/wk; 26 months	pulmonary tissue damage indicated by elevated lung alkaline phosphatases; progressive interstitial pneumonia only with higher concentration	Wagner et al., 1964 (105)
albino rats	10-125 mg/m^3 aerosol of spindle oil; 4 hr/day for 5 months	lowering of antibody titers to typhoid and paratyphoid vaccine; reduced phagocytic activity in blood of non-vaccinated rats	Bruskin, 1965 1965 (106)
30 rats	13, 30 or 60 mg/m^3 aerosols of industrial lubricating oils (without additives); 5 hr/day for 6 months	serum neuraminic acid levels increased progressively; decrease of serum albumin and leukocyte phogocytic activity; increased serum globulins	Lutov, 1973 (107)

TABLE 12 (Cont.)

Animal Toxicity of SGF No. 2 Models

D. Acute Oral Administration

Animal	Experimental Data	Results	Reference
mice	20 ml/kg of body weight/ day of white mineral oil ingested with diet	rough, dry skin; pilo-erection; restlessness; weight loss in 5 days; all died by 7-10 days; fatty degeneration of liver; proliferation of reticulo-endothelial cells of spleen; epidermal hyperkeratosis; renal tubular degeneration	Brahmachari, 1958 (102)
rats	5 ml/kg of body weight/ day of white mineral oil ingested with diet	same as above in mice	Brahmachari, 1958 (102)
1 monkey	2.2 ml/kg of body weight/ day of white mineral oil in diet; total consump-tion 96 ml	weight loss; diarrhea; death in 3 wk.; hepatic and renal congestion; ulceration and in-flammation of colon, heart, lung, spleen	Chadhuri and Chakravarty, 1952 (103)
1 monkey	1.1 ml/kg of body weight/ day of white mineral oil in duct; total consump-tion 36 ml	diarrhea; weight loss; death in 11 days; same pathological findings as above	Chadhuri and Chakravarty, 1952 (103)

E. Chronic Oral Administration

mice	ingestion of spindle oil following skin painting; 20-90 wk. (dose not specified)	"condition X" fatty in-filtration and degenera-tion of liver, spleen, ovary and adrenals	Twort and Twort, 1932 (110)
1 monkey	1.1 ml/kg of body weight/ day of white mineral oil in duct; total consump-tion 195 ml in 3 months	no adverse effects; slight hepatic and renal congestion	Chadhuri and Chakravarty, 1952 (103)

TABLE 12 (Cont.)

Animal Toxicity of SGF No. 2 Models

F. Skin Application

Animal	Experimental Data	Results	Reference
2 Holstein-Friesian calves	0.13 ml/kg of body weight/day of white lubricating oil for 8 weeks applied to skin	no gross skin pathology	Hoekstra et al., 1955 (25)
albino guinea pigs	0.6 ml/animal of white lubricating oil applied to skin every other day for 4 days	slight erythema and desquamation	Hoekstra and Phillips, 1963 (85)
albino guinea pigs	same for yellow lubricating oil	desquamation and hyperkeratosis	Hoekstra and Phillips, 1963 (85)

TABLE 13

Pulmonary Carcinogenicity of SGF No. 2 Models

Animal	Experimental Data	Results	Reference
20 mice	oil smoke exposure 16 times/month (no other data provided)	3 pulmonary neoplasms; 5 alveolar epithelializations; 4 other pulmonary lesions	Schepers, 1971 (112)
mice	mineral oil fumes (no other data provided)	no definite increase in tumor incidence	Twort and Twort, 1935 (100)
250 CAF_1/Jax mice	100 mg/m^3 aerosol of mineral oil; 6 hr/day; 5 days/wk for 16 months	equivocal evidence of altered rate of lung tumor formation in this tumor-susceptible species	Wagner et al., 1964 (105)
40 guinea pigs	aerosol of mineral oil; 24 exposures/month; (no other data provided)	1 pulmonary neoplasm; 8 alveolar epithelializations; 17 other pulmonary lesions	Schepers, 1971 (112)
40 guinea pigs	oil smoke; 24 exposures/month (no other data provided)	1 pulmonary neoplasm 4 alveolar epithelializations 9 other pulmonary lesions	Schepers, 1971 (112)

TABLE 14

Skin Carcinogenicity of SGF No. 2 Models

Animal	Experimental Data	Results	Reference
18 mice	50 mg/animal of 0.20% by weight white mineral oil with added benzo(a) pyrene applied 3 times/wk to dorsal skin until tumors appeared	non-accelerator for production of skin tumors	Horton et al., 1957 (113)
20 mice	100 mg/animal of alkyl-benzene mixtures applied 3 times/wk for 68 wk. to dorsal skin	no tumors developed	Horton et al., 1957 (113)
15 mice	50 mg/animal of acid treated lubricating oil applied 2 times/wk for 80 wk. to skin	9 malignant skin tumors; no benign tumors	Ellis, 1967 (62)
15 mice	same with a solvent refined oil	no tumors	Ellis, 1967 (62)
24 Chester-Beatty mice	0.25 ml/animal of batching oil applied to dorsal skin 2 times/wk for 84 wk.	6 skin malignancies 2 benign papillomas	Roe et al., 1967 (19)
50 C57 black mice	non-aromatic paraffin oil applied to nape of neck 2 times/wk for 24 months (dosage not specified)	mildly carcinogenic; 4 tumors developed	Heuper, 1960 (115)

IX. RECOMMENDATIONS

In any assessment of health aspects of exposure to a particular substance, it is of utmost importance to define the substance and the route or routes of exposure which are most likely to occur. Other factors which must be considered include the duration of exposure of personnel as well as relative health of individuals prior to exposure.

In dealing with fog oils, the following problems exist:

1. The physico-chemical nature of petroleum products is variable, depending on both the characteristics of the crude oils from which they were produced, and the refining processes which individual petroleum refineries employed in creating any one particular batch of either SGF No. 1 or SGF No. 2.

2. The generation of smoke screens from the oils, which involves vaporization of the oil and condensation of vapors into microdroplets of oil, is a process which (a) allows mixing of fog oil with exhaust fumes from the gasoline engine of the smoke generator itself, and (b) may permit some thermal decomposition of the oil during vaporization, both of which events will change the composition of the fog oil in a highly unpredictable manner.

3. There is difficulty in determining the concentration of the resultant fog oil smoke screen in the atmosphere, due to day-to-day changes in meteorological conditions such as wind speed, relative humidity and climatic temperature variation.

4. Personnel operating the smoke generators and handling the fog oils may be exposed to greater concentrations of oil smoke, or may be exposed for longer periods of time than personnel living under the smoke screen at a greater distance from its point of emergence from the generator.

5. Clinical symptoms, resulting from inhalation of the smoke, ingestion of oil which settles on food, and skin contact with oil which may contaminate clothing and exposed parts of the body, may be nonspecific, undiagnostic or otherwise impossible to attribute to oil smoke exposure, due to individual variation in personal hygiene and use of tobacco, among others.

These difficulties must be realized in attempts to design experimental exposures, as well as in analyzing the results of reported exposures. It was impossible to consider points 2 and 3, above, in this monograph, due to the lack of any available literature on these topics.

Recommendations for research on the chemical nature of fog oils and smoke generated from them include the following:

1. Analysis of the hydrocarbon composition of SGF No. 1 and No. 2 oils, and determination of other compounds (trace metals, nitrogen and sulfur compounds) present in them. It is helpful to delineate specific refinery procedures which were used in producing any one batch of fog oil, in that this knowledge will aid in correlating refining methods with chemical composition of the resultant oil. This can be of great value in determining the carcinogenic polycyclic aromatic hydrocarbons in SGF No. 2, for example. It is important to analyze as many different batches of SGF NO. 1 or SGF No. 2 as possible, in order to compare their compositions. If there is similarity, then further animal toxicological research (using a composite most nearly resembling the 'average' composition) may be useful.

2. Analysis of the smoke generated from fog oils, in terms of concentration of droplets in the atmosphere in mg/m^3, mean droplet diameter and percentage of respirable droplets ($<5\ \mu$) in the smoke, allowing for variation in meteorological conditions.

3. Determination of exhaust compounds present in the oil smoke, and relative concentrations of exhaust contaminants, using smoke generators under field conditions.

4. Study of the degree of thermal decomposition which can be expected and the nature and concentration of oil decomposition products in the resultant oil smoke.

5. In addition to elucidating the chemical nature of the fog oil smokes, this information must be applied in animal toxicological studies which more closely simulate field exposure conditions than past experiments which have been reported here. In the animal studies which should be considered to be undertaken, as listed in Table 1, the importance of recreating field conditions is emphasized. The only animal study which was ever reported for fog oil, utilized SGF No. 1 oil mists, in concentrations of 63 mg/m^3, in an exposure schedule of 30 minutes of every hour for 100 consecutive days (Lushbaugh et al., 1950). No studies have ever been reported for SGF No. 2.

6. Retrospective studies in humans exposed to fog oil smoke during World War II are warranted, in view of the documented skin carcinogenicity of some lubricating oils in humans who were occupationally exposed to them, as well as the uncertain report of gastric adenocarcinomas developing in monkeys exposed to SGF No. 1 oil mists. The thirty-year period which has elapsed since World War II may be sufficient to indicate trends in cancer incidence or mortality of exposed military personnel as well as populations neighboring the geographical locations of smoke screening operations, such as in Anzio, Italy, during the war.

In most epidemiologic studies performed to assess morbidity and mortality trends in workers exposed to industrial oils and mists, the determination of

significant predictors of morbidity and mortality has been complicated by social, psychological and constitutional factors. The same factors must be considered in any assessment of morbidity and mortality studies in personnel exposed to fog oil smokes.

TABLE 15.
Gaps in Toxicological Research in Animals

Compounds	SGF No. 1	SGF No. 1 Smoke	SGF No. 2	SGF No. 2 Smoke
PHASE I				
Acute oral LD_{50}	X		X	
Acute dermal LD_{50}	X		X	
Acute inhalation LC_{50}		X		X
Eye and skin irritation	X	X	X	X
Skin sensitization	X		X	
Metabolism in various animals[a]	X	X	X	X
Mutagenesis in microbes	X	X	X	X
PHASE II				
14-day feeding	X		X	
90-day feeding	X		X	
Sub-acute inhalation studies		X		X
PHASE III				
2-Year feeding[b]	X		X	
180-Day feeding	X		X	
Chronic inhalation studies		X		X
Fertility, reproduction	X	X	X	X
Teratology	X	X	X	X
Metabolism in various animals[c]	X	X	X	X

Notes: X-marks indicate that this study has not been undertaken.

[a] Including absorption, distribution, excretion, and biotransformation, using radio-labeled material.

[b] Including carcinogenicity evaluation.

[c] Including identification and possible isolation of any metabolites.

BIBLIOGRAPHY

1. James, B. (U.S. Army Contracting Officer; Defense Fuel Supply): Personal communication.

2. Military Specification: Fog oil. MIL-F-12070A, May 10, 1956.

3. Bland, W. F., R. L. Davidson: Petroleum processing handbook, McGraw-Hill, New York, 1967.

4. Popovich, M., C. Hering: Fuels and lubricants. John Wiley & Sons, Inc., New York, 1959.

5. Biscan, I. (U.S. Army Representive, Shell Oil Company, Houston, Texas): Personal communication.

6. Sachanen, A. N.: The chemical constituents of petroleum. Reinhold, New York, 1945.

7. Carpenter, C. P., D. L. Geary, Jr., R. C. Myers, D. J. Nachreiner, L. J. Sullivan, J. M. King: Petroleum hydrocarbon toxicity studies. XI. Animal and human response to vapors of deodorized kerosene. Toxicol Appl Pharmacol 36: 445-456, 1976.

8. Gerarde, H. W.: Toxicology and biochemistry of aromatic hydrocarbons. Elsevier, New York, 1960.

9. Snyder, L. R.: Routine determination of aromatic hydrocarbon types in catalytically cracked gas oils by linear elution adsorption chromatography. Anal Chem 36(4): 774-781, 1964.

10. Herlan, A.; [Hydrocarbon analysis of diesel fuels.] Erdoel Kohle, Erdgas, Petrochem 29(1): 32, 1976 (German).

11. Fodor, G. E., F. M. Newman: The application of high-performance liquid chromatography to the analysis of petroleum materials. Part 2. Quantitative hydrocarbon-type analysis. NTIS AD Rep. No. A014995, 1975.

12. Ehrler, A. J., R. E. Farrell, N. M. Ingber, T. M. Nawrocka: Analysis of kerosine and gas oils. Am Soc Testing Mater Spec Tech Publ No. 389: 188-213, 1965.

13. Kearns, G. L., N. C. Maranowski, G. F. Crable: Analysis of petroleum products in the C_{12}-C_{20} range. Application of FIA separatory and low voltage mass spectrometric techniques. Anal Chem 31(10): 1646-1651, 1959.

14. Keen, T. E. B.: The effect of petroleum distillates on lung surfactant. Aust Pediatr J 4: 229-235, 1968.

15. Fitzgerald, M. E., V. A. Cirillo, F. J. Galbraith: Mass spectrometric method for analysis of petroleum distillates in the furnace oil-kerosene boiling range: Anal Chem 34(10): 1276-1280, Sept. 1962.

16. Mair, B. J., T. J. Mayer: Composition of the dinuclear aromatics, C_{12}-C_{14}, in the light gas oil fraction of petroleum. Anal Chem 36(2): 351-362, 1964.

17. Gräf, W., C. Winter: [3,4-Benzpyrene in petroleum.] Arch Hyg Bakteriol 152(4): 289-293, 1968 (German).

18. Kipling, M. D., H. A. Waldron: Polycyclic aromatic hydrocarbons in mineral oil, tar, and pitch, excluding petroleum pitch. Prev Med 5(2): 262-278, 1976.

19. Roe, F. J. C., R. L. Carter, W. Taylor: Cancer hazard from mineral oil used in the processing of jute. Brit J Cancer 21(4): 694-702, 1967.

20. Thony, C., J. Thony, M. Lafontaine, J. C. Limasset: [Carcinogenic polycyclic aromatic hydrocarbons in petroleum products: Possible prevention of mineral oil cancer.] IARC Sci Pub 52(13): 165-170, 1976 (French).

21. Thiers, H.: [The general pathology of industrial oils.] Rev Lyon Mal 19: 15, Jan. 15, 1970 (French).

22. Klauder, J. V., F. A. Brill, Jr.: Correlation of boiling ranges of some petroleum solvents with irritant action on skin. Arch Dermatol Syphilol 56: 197-215, 1947.

23. Cook, J. W., W. Carruthers, D. L. Woodhouse: Carcinogenicity of mineral oil fractions. Brit Med Bull 14(2): 132-135, 1958.

24. Goldstein, D. H., J. N. Benoit, H. A. Tyroler: An epidemiologic study of an oil mist exposure. Arch Environ Health 21(5): 600-603, 1970.

25. Hoekstra, W. G., R. J. Dicke, P. H. Phillips: Further studies on the production of a hyperkeratosis in calves with topically applied base-oils for use in livestock sprays. J Dairy Sci 38: 186-193, 1955.

26. Martindale: The Extra Pharmacopoea. 26th ed. The Pharmaceutical Press, London, 1973, pp. 1273-1275.

27. Wagner, W. O., O. J. Dobrogorski, H. E. Stokinger: Antagonistic action of oil mists on air pollutants. Arch Environ Health 2(5): 523-534, 1961.

28. Boitnott, J. K., S. Margolis: Mineral oil in human tissues. II. Oil droplets in lymph nodes of the porta hepatis. Bull Johns Hopkins Hosp 118: 414-422, May 1966.

29. Hasserholt, U., O. Lehmann: Mineral oil products. Method Chim 1(Pt. B): 944-970, 1974.

30. Puro, T. E.: Chemical warfare: smokes. Kirk Othmer, Encyclopedia of Chemical Technology. Interscience Publishers, New York, 1966, 2nd ed., Vol. 4, pp. 900-906.

31. Department of the Army and the Air Force: Military chemistry and chemical agents. Technical Manual No. 3-215/Air Force Manual No. 355-7, Dec. 6, 1963, pp. 49-50.

32. Military Specification: Smoke pot, floating, SGF2, AN-M7A1. MIL-S-51235B, Feb. 5, 1974.

33. Levey, H. A.; Chemical smokes and smoke screens. Chem Industries 58: 980-981, 1044, 1946.

34. Army: Generator, smoke, mechanical, pulse jet, M3A3. Technical Manual TM 3-1040-202-12, Dec. 1975.

35. Anonymous: Fire and explosion hazards of thermal insecticidal fogging. National Board of Fire Underwriters, NBFU Research Report 9, 45 pp., 1952.

36. Klaus, E. E., J. M. Perez: Thermal stability characteristics of some mineral oil and hydrocarbon hydraulic fluids and lubricants. ASLE Transactions 10: 38-47, 1967.

37. Brophy, L. P. (Command Historian, U.S. Army Munitions Command, Dover, New Jersey): Memorandum: Historical investigation of possible injurious effects of fog oil in smoke screens. June 10, 1963.

38. Butler, C. A. (Acting Assistant Chief, U.S. Army Munitions Systems Division, Development and Engineering Directorate): Conversation record: Request for information on fog oil. Feb. 21, 1974.

39. McNamara, B. P. (Chief, Toxicology Division, U.S. Army Edgewood Arsenal): Effects from exposure to aerosols of fog oil. June 7, 1963.

40. Dautrebande, L., R. Capps: Studies on aerosols. IX. Enhancement of irritating effects of various substances on the eye, nose and throat by particulate matter and liquid aerosols in connection with pollution of the atmosphere. Arch Int Pharmacodyn Ther 82(4): 505-528, 1950.

41. Nau, C. A., J. Neal, M. Thornton: C_9-C_{12} fractions obtained from petroleum distillates. An evaluation of their potential toxicity. Arch Environ Health 12: 382-393, March 1966.

42. Il'in, B. I., L. I. Kogan, N. V. Buzulutskii: [Suppurative diseases in persons working with fuels and lubricants.] Voen Med Zh 9: 69, 1969 (Russian).

43. Barnes, R. L., D. S. Wilkinson: Epidermal necrolysis from clothing impregnated with paraffin. Br Med J 4: 466-467, 1973.

44. Yaxley, R. P.: Medical memoranda. Diesel-oil injection injuries. Br Med J 5200: 714-715, Sept. 3, 1960.

45. Lejeune, E., G. Moulin, L. Cotte: [Symptomatology of dyspepsias from absorption of caustic agents. Apropos of a case of gastritis following fuel-oil ingestion.] Arch Mal Prof Med Trav Secur Soc 22(3): 167, 1961 (French).

46. Olsen, A. M.: The spectrum of aspiration pneumonitis. Ann Otol Rhinol Laryngol 79(5): 875-878, 1970.

47. Szamosi, J., M. Hornyák, M. Burkovits: [Gasoline, kerosene and diesel fuel poisoning in children in clinical practice.] Orv Hetil 116(21): 1209-1212, 1975 (Hungarian).

48. Haraszti, A., M. Sóvári: [Fatal pulmonary gangrene caused by inhalation of fuel oil.] Orv Hetil 109(16): 851-854, 1968 (Hungarian).

49. Engebrigtsen, J. K.: [Dermatoses caused by diesel oil among workers in an asbestos-cement factory.] Nord Hyg Tidskr 9: 250-255, 1951 (Swedish).

50. Rao, M. V.: Industrial dermatitis due to diesel oil - a study of 25 cases. Indian J Dermatol Venereol 38(4): 146-149, 1972.

51. Laignel-Lavastine, M., A. F. Liber: [Toxic disturbances of skin and nervous system in a diesel truck driver.] Presse Med 42: 1578-1580, 1934 (French).

52. Fischer, H. G. M., W. Priestley, Jr., L. T. Ely, G. G. Wanless, J. Rehner, Jr.: Properties of high-boiling petroleum products. Physical and chemical properties as related to carcinogenic activity. Arch Ind Hyg Occup Med 4: 315-324, 1951.

53. Waterhouse, J. A.: Lung cancer and gastro-intestinal cancer in mineral oil workers. Ann Occup Hyg 15: 43-44, 1972.

54. Grupinski, L., W. Oblander, K. Neuschwander, W. Staub: [Measuring workplace atmosphere oil concentrations.] Arbeitsschutz 1: 12-17, 1972 (German).

55. Hervin, R. L., J. Lucas: Health hazard evaluation/toxicity determination. U.S. Nat Tech Inform Serv, PB Rep. 229645/76A, 1973.

56. Drasche, H., L. Finzel, H. Martschei, R. Meyer: [Industrial-medical investigations of persons exposed to oil mists.] Zentralbl Arbeitsmed 24(10): 305-312, 1974 (German).

57. Hendricks, N. V., G. H. Collings, A. E. Dooley, J. T. Garrett, J. B. Rather, Jr.: A review of exposures to oil mist. Arch Environ Health 4: 21-27, 1962.

58. Despierres, G., P. A. Bonnet, H. Phelip, M. Piante: [Alveolar carcinoma and inhalation of industrial oils.] J Fr Med Chir Thorac 19(5): 561-567, 1965 (French).

59. Hodgson, G.: Codes of practice relating to metal working fluids. Health problems arising from contact and exposure of workers to metal working fluids. J Inst Petrol 59(565): 1-8, Jan. 1973.

60. Parkes, H. G.: Cancer and exposure to mineral oils. Ind Med 39(2): 78-81, 1970.

61. Ayer, H. E.: Sampling methods for oil mist in industry. Amer Industr Hyg Assoc J 25: 151-157, Mar.-Apr. 1964.

62. Ellis, E. G.: Lubricants: An industrial health hazard? Ind Lubric 19(4): 141-145, 1967.

63. Waldron, H. A.: The carcinogenicity of oil mist. Br J Cancer 32(2): 256-257, 1975.

64. Morris, G. E., C. Maloof: Causes of cutting-oil dermatitis. N Engl J Med 247(9): 440-441, 1952.

65. Decoufle, P.: Cancer mortality among workers exposed to cutting-oil mist. Ann N Y Acad Sci 271: 94-101, May 28, 1976.

66. Falk, H. L., P. Kotin, A. Mehler: Polycyclic hydrocarbons as carcinogens for man. Arch Environ Health 8(5): 721-729, 1964.

67. Bryan, C. S., J. K. Boitnott: Adenocarcinoma of the lung with chronic mineral oil pneumonia. Am Rev Resp Dis 99: 272-274, Feb. 1969.

68. Sante, L. R.: The fate of oil particles in the lung and their possible relationship to the development of bronchogenic carcinoma. Am J Roentgenol 62: 788-797, 1949.

69. Shoshkes, M., W. G. Banfield Jr., S. J. Rosenbaum, A. J. Fisk: Distribution, effect and fate of oil aerosol particles retained in the lungs of mice. Arch Ind Hyg Occup Med 1: 20-35, 1950.

70. Andreeva-Galanina, E. Ts., Z. Z. Bruskin: [Effect of inhaling oil aerosols.] Gig Sanit 29(3): 70-73, 1964 (Russian).

71. Miller, A., R. A. Bader, M. E. Bader, A. S. Teirstein, I. J. Selikoff: Mineral oil pneumonia. Ann Int Med 57: 627-634, 1962.

72. Nickol, K. H.: Letter - Hazard of mineral-oil mist? Lancet 2(684): 1184-1185, 1970.

73. Bruskin, Z. Z., V. G. Demchenko: [External respiration and gas metabolism in workers exposed to the effect of lubricating oil aerosols.] Gig Tr Prof Zabol 4: 28-30, 1975 (Russian).

74. Ely, T. S., S. F. Pedley, F. T. Hearne, W. T. Stille: A study of mortality, symptoms, and respiratory function in humans occupationally exposed to oil mist. J Occup Med 12(7): 253-261, 1970.

75. Ankermuller, F. M.: [On prophylaxis for prevention of occupational dermatoses, especially to oil acne.] Med Welt 38: 1988-1991, Sept. 17, 1960 (German).

76. Anonymous: Cancer from mineral oil. Br Med J (5681): 443-444, Nov. 22, 1969.

77. Pasternack, B., L. Ehrlich: Occupational exposure to an oil mist atmosphere: a 12-year mortality study. Arch Environ Health 25(4): 286-294, 1972.

78. Berlin, C.: Acne comedo in children due to paraffin oil applied on the head. AMA Arch Dermat Syph 69(6): 683-687, 1954.

79. Meyers, J. B., R. L. Griffith: Lipid pneumonia due to prolonged ingestion of mineral oil. Dis Chest 27: 677-684, 1955.

80. Becker, G. L.: The case against mineral oil. Amer J Digest Dis 344-348, Nov. 1952.

81. Barzó, P., I. Gyulai, J. Schnitzler: [Pulmonary lesions due to aspiration of mineral oil.] Prax Pneumol 27(4): 216-225, 1973 (German).

82. Casey, J. F.: Chronic cor pulmonale associated with lipoid pneumonia. JAMA 177: 896-898, Sept. 30, 1961.

83. Prigal, S. J.: Mineral oil as a human carcinogen, fact and fiction. Ann Allergy 25(8): 449-461, 1967.

84. Rebello, D. J. A., R. R. Suskind: The effect of common contactants on cutaneous reactivity to sensitizers. J Invest Dermatol 41: 67-80, 1963.

85. Hoekstra, W. G., P. H. Phillips: Effects of topically applied mineral oil fractions on the skin of guinea pigs. J Invest Dermatol 40: 79-88, Feb. 1963.

86. Boitnott, J. K., S. Margolis: Mineral oil in human tissues. I. Detection of saturated hydrocarbons using thin-layer chromatography. Bull Johns Hopkins Hosp 118(5): 402-413, 1966.

87. Boitnott, J. K., S. Margolis: Saturated hydrocarbons in human tissues. III. Oil droplets in the liver and spleen. Johns Hopkins Med J 127: 65-78, Aug. 1970.

88. Bayer, P. M., R. Dudczak, H. Fuchs: [Mineral oil pneumonia caused by nasal drops containing liquid paraffin. Diagnosis by examination of the sputum.] Wien Klin Wschr 86(15): 438-441, 1974 (German).

89. Lushbaugh, C. C., J. W. Green, C. E. Redemann: Effects of prolonged inhalation of oil fogs on experimental animals. Arch Ind Hyg Occup Med 1: 237-247, 1950.

90. Lushbaugh, C. C., C. E. Redemann, J. Savit: The intrapulmonic accumulation and effects of inhaled lubricating oil and SGF No.1 oil in monkeys. University of Chicago Toxicity Laboratory Report No. 46, 1945.

91. Samal, U. C., R. Saran, R. K. Sanyal: Effects of inhaled fumes on immunological response of rabbits. Indian J Physiol Pharmacol 19(2): 103-104, 1975.

92. Starek, A., L. Fiema, D. Cembala, W. Lepiarz: [Comparing toxicity of certain oil products used as dielectrics in electroerosive working. I. Acute and subacute toxicity.] Med Pr 26(3): 219-230, 1975 (Polish)

93. Gerarde, H. W.: Toxicological studies on hydrocarbons. IX. The aspiration hazard and toxicity of hydrocarbons and hydrocarbon mixtures. Arch Environ Health 6: 329-341, 1963.

94. Tani, K.: [The effect of various petroleum fractions on rabbit blood sugar.] Okayama Igakkai Zassi 5: 84-90, 1939 (Japanese).

95. Messerli, W.: [Poisoning by diesel oil in a herd of cattle.] Schweiz Arch Tierheilkd 111(11): 642-644, 1969 (German).

96. Ranger, S. F.: A case of diesel oil poisoning in a ewe. Vet Rec 99(25-2): 508-509, 1976.

97. Starek, A., W. Lepiarz, B. Oginska: [Comparative studies on the toxicity of certain dielectrics derived from petroleum and used in electroerosive working. II. Topical acute and subacute toxicity.] Med Pr 27(2): 77-89, 1976 (Polish).

98. Starek, A., D. Cembala: [Toxicity of petrochemical dielectrics used in electroerosive treatment of metals on cutaneous application to rats.] Med Pr 25(2): 187-192, 1974 (Polish).

99. Bien, E., P. Buntrock: [Action of various petroleum fractions on experimental wound granulation.] Pharmazie 24(10): 629-632, 1969 (German).

100. Twort, C. C., J. M. Twort: Induction of cancer by cracked mineral oils. Lancet II: 1226-1228, 1935.

101. Eckert, H., D. Kandt: [Morphological changes in experimental lipid pneumonia.] Z Erkr Atmungsorgane 142(1): 59-67, 1975 (German).

102. Brahmachari, H. D.: Toxicity of white oil. Current Sci 27(11): 440-441, 1958.

103. Chaudhuri, R. N., N. K. Chakravarty: Observations on the toxicity of white oil. Indian J Med Sc 6(2): 137-139, 1952.

104. Lushbaugh, C. C., P. R. Cannon: Toxicity and incidence of lipid pneumonia upon inhalation of automobile oil (SAE No. 10) cloud. University of Chicago Toxicity Laboratory Report No. 9, 1942.

105. Wagner, W. D., P. G. Wright, H. E. Stokinger: Inhalation toxicology of oil mists. I. Chronic effects of white mineral oil. Amer Ind Hyg Assoc J 25(2): 158-168, 1964.

106. Bruskin, Z. Z.: [The effect of lubricating oil aerosols upon the immunological reactivity of the animal organisms.] Gig Tr Prof Zabol 9(10): 7-11, 1965 (Russian).

107. Lutov, V. A.: [Effect of aerosols of additive-free petroleum oils on immunological activity of animals.] Gig Sanit 3: 117-118, 1973 (Russian).

108. Lutov, V. A.: [Data on the substantiation of maximum allowable concentrations of petroleum-derived additive-free oil aerosols used as lubricant-coolant fluids.] Gig Tr Prof Zabol 10: 49-52, Oct. 1974 (Russian).

109. Eckardt, R. E.: Petroleum and petroleum products. In Encyclopedia of occupational health and safety, McGraw Hill, New York, 1976, pp. 1027-1031.

110. Twort, J. M., C. C. Twort: Changes in the liver of mice following the ingestion of hydrocarbon oils. Lancet 1: 448-449, 1932.

111. Vamos, E.: [Skin tolerance to the mineral oil components of white oil.] Schmierstoffe Schmierungstech 16: 80-84, 1967 (German).

112. Schepers, G. W. H.: Lung tumors of primates and rodents. Part II. Ind Med Surg 40(2): 23-31, 1971.

113. Horton, A. W., D. T. Denman, R. P. Trosset: Carcinogenesis of the skin. II. The accelerating properties of aliphatic and related hydrocarbons. Cancer Res 17(8): 758-766, 1957.

114. Horton, A. W.: Investigation of the cellular mechanisms of chemical carcinogenesis. U. S. Nat Tech Inform Serv, PB Rep, issue 225631/1GA, 1973.

115. Hueper, W. C., W. W. Payne: Carcinogenic studies on petroleum asphalt, cooling oil, and coal tar. AMA Arch Pathol 70: 372-384, 1960.

116. El Mahdi, M. A. H., H. J. Channon: The absorption of n-hexadecane from the alimentary tract of the rat. Biochem J 27: 1487-1494, 1933.

117. Stetten, Jr., D.: Metabolism of a paraffin. J Biol Chem 147: 327-332, 1943.

118. Bernhard, K., U. Gloor, E. Scheitlin: [Dehydrogenations which precede the biological degradation of the carbon chain. Dehydrogenations of hydrocarbons and fatty acids in the intestinal wall.] Hoppe-Seyler's Z Physiol Chem 299: 235-239, 1955 (German).

119. McCarthy, R. D.: Mammalian metabolism of straight-chain saturated hydrocarbons. Biochim Biophys Acta 84: 74-79, 1964.

120. Mitchell, M. P., G. Hübscher: Oxidation of n-hexadecane by subcellular preparations of guinea pig small intestine. Eur J Biochem 7(1): 90-95, 1968.

121. Albro, P. W., L. Fishbein: Absorption of aliphatic hydrocarbons by rats. Biochim Biophys Acta 219: 437-446, 1970.

122. Rossmiller, J. D., W. G. Hoekstra: Hexadecane-induced hyperkeratinization of guinea pig skin. III. Cutaneous penetration of topically applied hexadecane-1-^{14}C. J Invest Dermatol 47(1): 39-43, 1966.

123. Widhalm, K., J. Deutsch, G. Weissenbacker: [Proceedings: Renal excretion of mineral oil constituents in fuel oil intoxication.] Munch Med Wochenschr 116(32-33): 1452, 1974 (German).

124. Bernhard, K.: Absorption of aliphatic hydrocarbons, carotene, and vitamin A by the rat. Fette Seifen 55: 160-166, 1953 (German).

125. Popovic, M.: The metabolism of paraffins in rats. FEBS Lett 12(1): 49-50, 1970.

126. Kusonose, M., K. Ichihara, E. Kusunose: Oxidation of n-hexadecane by mouse liver microsomal fraction. Biochim Biophys Acta 176: 679-681, 1969.

127. Deichmann, W., G. Thomas: Glucuronic acid in the urine as a measure of the absorption of certain organic compounds. J Ind Hyg Toxicol 25: 286-292, 1943.

128. Daly, J. W., D. M. Jerina, B. Witkop: Arene oxides and the NIH shift. Experientia (Basel) 28(10): 1129-1149, 1972.

129. Stryker, W. A.: Absorption of liquid petrolatum ("mineral oil") from the intestine. Arch Path 31: 670-692, 1941.

130. Ebert, A. G., C. R. Schleiffer, S. M. Hess: Absorption, disposition and excretion of ^{3}H-mineral oil in rats. J Pharm Sci 55: 923-929, 1966.

131. Buhrer, G., S. Widgren: [Effects of mineral oil in the rabbit. III. Radiochemical and histologic study of distribution after intravenous administration.] Arch Int Pharmacodyn 144(3-4): 355-361, 1963 (French).

132. Wislocki, P. G., A. W. Wood, R. L. Chang, W. Levin, H. Yagi, O. Hernandez, P. M. Dansette, D. M. Jerina, A. H. Conney: Mutagenicity and cytotoxicity of benzo(a)pyrene arene oxides, phenols, quinones, and dihydrodiols in bacterial and mammalian cells. Cancer Res 36: 3350-3357, 1976.

133. Jerina, D. M., J. W. Daly: Arene oxides: A new aspect of drug metabolism. Science 185(4151): 573-582, 1974.

134. Military Specification: Mask, Protective, Field. ABC-M17 MIL-M-0050079E(MU), 1968.

135. Plunkett, R.: Diesel engine dermatitis control. Minn Med 37(5): 336-338, 1954.

136. Anonymous: Fed Reg 39(202): 23540, 1974.

137. Berner, A.: [Measuring deposition of dioctyl phthalate and paraffin oil aerosols in the Goetz aerosol spectrometer.] Staub-Reinhalt Luft 26(7): 306-308, 1966 (German).

138. Ol'khovskaia, Z. K.: [Colorimetric method for the determination of the hydrocarbons gasoline, white spirit and kerosene in the air of industrial workplaces.] Gig Tr Prof Zabol 15(11): 57-58, 1971 (Russian).

139. Turner, D., H. G. Baxter, G. M. Davies, A. R. Eyres, G. L. Lees, J. Mitchell, J. T. Sanderson, J. Steel, J. P. Moore (Institute of Petroleum Occupational Hygiene Subcommittee): Methods for the determination of the atmospheric concentration of oil mist. Ann Occup Hyg 18(4): 293-297, 1975.

140. Gerarde, H. W., P. Skiba: Toxicological studies on hydrocarbons. VI. A colorimetric method for the determination of kerosine in blood. Clin Chem 6: 327-331, 1960.

141. Lutov, V. A.: [Determining the concentration of oil aerosols in the air of industrial installations by the gravimetric method with the aid of FPP-15 filters.] Gig Tr Prof Zabol 8(2): 53-55, 1964 (Russian).

142. Atlasov, A. G.: [Methods of sampling mineral oil aerosols.] Gig Tr Prof Zabol 8: 60-61, 1975 (Russian).

143. Asset, G., M. A. Ross, S. Ryan: Effects of inhalation of aerosols of three engine oils (U). U. S. Army Chemical Warfare Laboratories Technical Report CWLR 2068, March 1958.

144. Chand, S., C. Srinivasulu, S. N. Mahapatra: Detection of mineral oils in edible oils by thin-layer chromatography. J Chromatogr 106: 475-476, 1975.

APPENDIX

INFORMATION SOURCES EXAMINED

Computer Searchable Data Bases

1. National Technical Information Services - covering 1964 to present (searched on 4/4/77)
2. TOXLINE/TOXBACK (searched on 3/29/77)
3. Chemical Condensates - covering 1972 to present (searched on 4/1/77)
4. BIOSIS Previews - covering 1972 to present (searched on 4/8/77)
5. ISI SCISEARCH - covering 1974 to present (searched on 4/8/77)
6. CANCERLINE (searched on 5/5/77)
7. NIOSH Technical Information Center file - (received on May 15, 77)
8. American Petroleum Institute file - (received on May 15, 77)
9. Defense Documentation Center - (received on May 15, 77)

Hardbound Secondary References

1. Chemical Abstracts - V.1 (1907) - V.83 (1975).
2. Index Medicus - V.1 (1927) - V.18 (No. 4), 1977.
3. Excerpta Medica - sections entitled *Toxicology and Pharmacology, Occupational Health and Industrial Medicine, Cancer, Environmental Health and Pollution Control* (covering Vol. 1 through last volume available in 1976) were examined.
4. Engineering Index - (covering 1940 through 1977, issue #3).
5. Biological Abstracts - [covering Vol. 1 (1927) through Vol. 61 1976)].

Other References Examined

1. Gleason, M. N., R. E. Gosselin, H. C. Hodge, R. P. Smith, Clinical Toxicology of Commercial Products, Williams & Wilkins, Baltimore, 1969, 3rd Ed.
2. Browning, E., Toxicity & Metabolism of Industrial Solvents, Elsevier Publishing Company, New York, 1965.

3. API Toxicological Reviews, American Petroleum Institute, New York, N. Y.

4. Goodman, L. S., A. Gilman, The Pharmacological Basis of Therapeutics, The Macmillan Company, New York, 1970 (Fourth Edition).

5. Code of Federal Regulations, July 1, 1976.

6. AIHA Hygiene Guide, Cincinnati, American Industrial Hygiene Association.

7. Parke, D. V., Biochemistry of Foreign Compounds, Pergamon Press, Oxford, 1968.

8. Shepard, T. H., Catalog of Teratogenic Agents, The Johns Hopkins University Press, Baltimore, 1973.

9. Fishbein, L., Chromatography of Environmental Hazards, Vol. 2, Elsevier Publishing Company, New York, 1973.

10. Thienes, C. L., T. J. Haley, Clinical Toxicology, Lea and Febiger, Philadelphia, 1972 (Fifth Edition).

11. Sax, N. I., Dangerous Properties of Industrial Materials, van Nostrand Reinhold Co., New York, 1975.

12. American Conference of Governmental Industrial Hygienists, Documentation of the Threshold Limit Values for Substances in Workroom Air, 1971 (Third Edition).

13. International Labour Office, Encyclopedia of Occupational Health and Safety, McGraw-Hill Book Co., New York, 1971-1972.

14. The Chemical Society, Foreign Compounds Metabolism in Mammals, Vol. 1 & 2, The Chemical Society, London, 1970 and 1972.

15. Committee on the Handbook of Biological Data, National Academy of Sciences, National Research Council, Washington, D. C., Handbook of Toxicology, Vol. 1-5, W. B. Saunders Co., Philadelphia, 1959.

16. World Health Organization, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 1-12, WHO, International Agency for Research on Cancer, Lyon.

17. Patty, F. A. (Ed.), Industrial Hygiene and Toxicology, Interscience Publishers, New York, 1963, second revised edition, Vol. 2.

18. Hamilton, A., H. L. Hardy, Industrial Toxicology, Publishing Sciences Group, Inc., Acton, Mass., 1974 (Third Edition).

19. Kirk-Othmer, Encyclopedia of Chemical Technology, Interscience Publishers, New York, 1972 (Second Edition).

20. Stecher, P. G., Merck Index, Merck & Co., Rahway, N. J., 1968 (Eighth Edition).

21. Arena, J. M., Poisoning-Toxicology-Symptoms-Treatments, Charles C. Thomas Publisher, Springfield, Illinois, 1974 (Third Edition)

22. National Institute for Occupational Safety and Health, Registry of Toxic Effects of Chemical Substances, Government Printing Office, Washington, D. C., 1975.

23. National Cancer Institute, Survey of Compounds which have been tested for Carcinogenic Activity, DHEW Publication No. (NIH) 73-453, Rockville, Md., 1973 (all volumes through 1972-73 volume).

24. The International Technical Information Institute, Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data, International Technical Information Institute, Tokyo, 1975.

Organizations Contacted

1. American Petroleum Institute, Washington, D. C.

2. National Institute of Occupational Safety and Health, Cincinnati, Ohio.

3. U.S. Army Environmental Hygiene Agency, Edgewood Arsenal, Md.

4. U.S. Army Mobility Equipment R&D Center, Fuels & Lubricants, Petroleum & Materiel Dept., Ft. Belvoir, Va.

5. U.S. Army Fuels & Lubricants Research Laboratory, Southwest Research Institute, San Antonio, Texas.

6. Naval Environmental Hygiene Center, Cincinnati, Ohio.

7. U.S. Navy Medical R&D Command, National Naval Medical Center, Bethesda, Md.

8. Advisory Center for Toxicology, National Academy of Sciences, Washington, D.C.

9. FMC Corporation, Ordnance Engineering Division, San Jose, Calif.

10. Teledyne Continental Motors, General Products Division, Muskegon, Michigan.

11. U.S. Army Defense Fuel Supply Agency, Washington, D.C.

12. Shell Oil Company, Houston, Texas.

Persons Contacted

1. Baker, Lt. Charles,
   Bureau of Medicine & Surgery
   Dept. of the Navy
   Washington, D. C. 20372
   (202)-254-4384

2. Baumel, Dr.
   NIOSH
   Rockville, Maryland
   (301)-443-5290

3. Carpenter, Dr. C. P.
   Carnegie-Mellon Institute of Research
   Carnegie-Mellon University
   Pittsburgh, Pa. 15213
   (412)-327-1020

4. Crawl, Mr. James
   U.S. Naval Environmental Hygiene Center
   Cincinnati, Ohio

5. Doptis, Lt. Commander Leigh
   Naval Medical R&D Command
   National Naval Medical Center
   Bethesda, Maryland 20014
   (301)-295-1131 or (301)-295-1028

6. Hathaway, Lt. Col. James
   U.S. Army Environmental Hygiene Agency
   Edgewood Arsenal, Maryland
   (301)-671-2304

7. Holdsworth, Dr. Charles, Toxicologist
   Health Affairs
   American Petroleum Institute
   Washington, D. C.
   (202)-457-7182

8. Johnston, Mr. Allan
   U.S. Army Fuels & Lubricants Research Labs.
   Southwest Research Institute
   San Antonio, Texas
   (512)-684-5111

9. Le Pera, Mr.
   Fuels & Lubricants
   Petroleum & Materiel Department
   U.S. Army Mobility Equipment R&D Center
   Ft. Belvoir, VA
   (703)-664-3113

10. Martinez, Miss Clara
American Petroleum Institute
275 Madison Avenue, 9th Floor
New York, N. Y. 10016
(212)-685-1349

11. Miller, Mr. Lester
Chemical Systems Lab.
U.S. Army Environmental Hygiene Agency
Edgewood Arsenal, Maryland
(301)-671-3557

12. Orrel, Mr. John
FMC Corporation
Ordnance Engineering Division
1105 Coleman Ave.
San Jose, Calif. 95108
(408)-289-0111

13. Owens, Mr. Ed
Chemical Systems Lab.
U.S. Army Environmental Hygiene Agency
Edgewood Arsenal, Maryland
(301)-671-2129

14. Richardson, Lt.
Ft. Sheridan, Illinois
(312)-926-2258

15. Stokinger, Dr. Herbert
Chief Toxicologist
NIOSH
Cincinnati, Ohio 45202
(513)-684-8392

16. Taft, Mr. Richard
NIOSH
DTS, COSHI, IRAS, C-19
4676 Columbia Parkway
Cincinnati, Ohio 45226

17. Wilson, Mr. Richard
Teledyne Continental Motors,
General Products Division
76 Getty Street,
Muskegon, Michigan 49442
(616) - 734-2867

18. Winstead, Dr. Jack
Advisory Center for Toxicology
National Academy of Sciences
Washington, D. C.
(202)-393-8100

19. Mr. Hall
American Petroleum Institute
Washington, D.C.
(202)-457-7000

20. Mr. Faber
U.S. Army Defense Fuel Supply Agency
Washington, D.C.
(202)-545-6700 or (202)-284-7500

21. Mr. Bob James
U.S. Army Contracting Officer
U.S. Army Defense Fuel Supply Agency
Washington, D. C.
(202)-274-7461

22. Mr. Ivin Biscan
U.S. Government Representative
Shell Oil Company
Houston, Texas
(713)-241-4201